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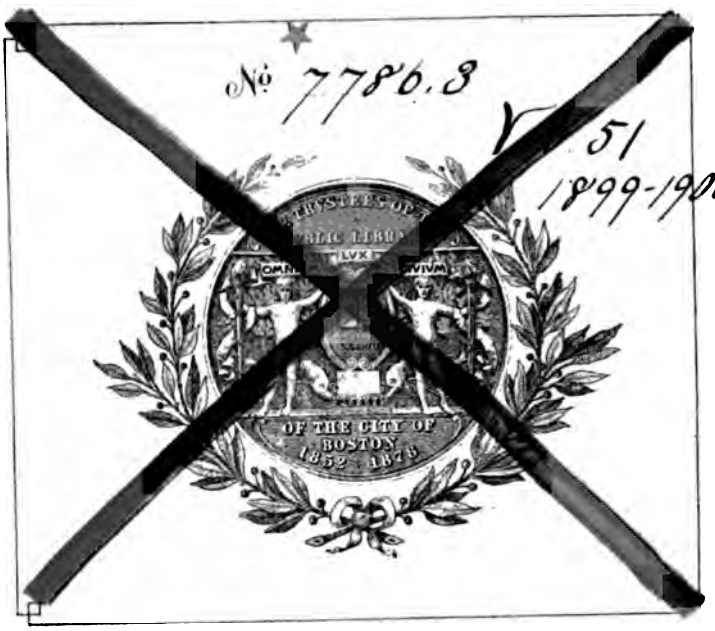

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OF THE

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VOLUME THE FIFTY-FIRST.

COMPRISING THE REPORT OF THE PROCEEDINGS FOR THE SESSION 1899–1900.

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1861 **COUPER**, JOHN, 80, Grosvenor street, W. (C. 1870-2.)

1873 **COUPLAND**, SIDNEY, M.D. (TREASURER), 16, Queen Anne street, W. (M.G.C. 1882-6. C. 1878-81, 1889-91. S. 1886-8. V.-P. 1892-3. T. 1894—.)

1897 CRAWFURD, RAYMOND H. P., M.D., 71, Harley street, W.

1884 CRICHTON, GEORGE, M.D., 96, Earl's Court road, W.

1873 CRIPPS, WILLIAM HARRISON, 2, Stratford place, W. (C. 1883-5. V.-P. 1893-4.)

1877 **CROCKER**, HENRY RADCLIFFE, M.D., 121, Harley street, W. (C. 1887-9. V.-P. 1897-9.)

1856 CROFT, JOHN, 6, Mansfield street, W. (C. 1870-2. V.-P. 1882-4.)

1886 CROOKSHANK, EDGAR, M.B., Saint Hill, East Grinstead, Sussex. (C. 1890-3. V.-P., 1900—.)

1875 CROSS, FRANCIS RICHARDSON, 5, The Mall, Clifton, Bristol.

1890 CROWLE, THOMAS H. RICKARD, 35, St. James's place, S.W.

1889 CUFF, ROBERT, M.B., 1, The Crescent, Scarborough.

1885 CULLINGWORTH, CHARLES JAMES, M.D., 14, Manchester square, W.

1871 CUMBERBATCH, A. ELKIN, 80, Portland place, W.

1893 CURTIS, HENRY JONES, M.D., 30, Harley street, W.

1884 DAKIN, W. RADFORD, M.D., B.S., 18, Grosvenor street, Grosvenor square, W.

1883 DALTON, NORMAN, M.D., 4, Mansfield street, W.

1873 DAVIDSON, ALEXANDER, M.D., 2, Gambier terrace, Liverpool.

1883 DAVIS, EDWIN HARRY, West Hartlepool.

1859 **Davis**, FRANCIS WILLIAM, R.N.

1879 DAVY, HENRY, M.D., 29, Southernhay, Exeter.

1894 DAWSON, BERTRAND, M.D., 110, Harley street, W.

1899 DEAN, GEORGE, M.D., The Jenner Institute of Preventive Medicine, The Poplars, Sudbury, Harrow.

1889 DEAN, HENRY PERCY, M.B., M.S., 69, Harley street, W. (C. 1900—.)

1899 DE CHAZAL, EDMOND LUCIEN, M.D., Port Louis, Mauritius.

1887 DELÉPINE, SHERIDAN, M.B., C.M., Owens College, Manchester. (C. 1899—.)

1880 DENT, CLINTON T., 61, Brook street, W.

1871 DICKINSON, EDWARD HARRIMAN, M.A., M.D., 51A, Rodney street, Liverpool.

1858 **DICKINSON**, WILLIAM HOWSHIP, M.D., 9, Chesterfield street, W. (C. 1866-8. S. 1869-71. V.-P. 1872-4. P. 1889-90.)

1890 **DICKINSON**, WILLIAM LEE, M.D., 9, Chesterfield street, W.

1872 DIVER, EBENEZER, M.D., Garstone, St. Margaret's-on-Thames, Twickenham.

1872 DORAN, ALBAN HENRY GRIFFITHS, 9, Granville place, W. (C. 1882-4. V.-P. 1894-6.)

1866 DOUGLAS-POWELL, Sir RICHARD, Bart., M.D., 62, Wimpole street, W. (C. 1873-5, 1881-3. S. 1877-9. V.-P. 1887-8.)

Elected

1893 DOWSON, WALTER, M.D., 46, Alleyn road, West Dulwich.

1877 DRAKE-BROCKMAN, EDWARD F., 14, Welbeck street, W.

1880 DRESCHFELD, JULIUS, M.D., 3, St. Peter's square, Manchester. (C. 1896-9.)

1896 DREW, DOUGLAS, M.B., 39, Devonshire street, Portland place, W.

1879 DREWITT, F. G. DAWTREY, M.D., 14, Palace gardens terrace, Kensington, W. (C. 1890-2.)

1893 DRYSDALE, JOHN HANNAH, M.D., 25, Welbeck street, W.

1865 **DUCKWORTH**, Sir DYCE, M.D., LL.D., 11, Grafton street, Bond street, W. (C. 1877.)

1847 **DUDGEON**, ROBERT E., M.D., 63, Upper Berkeley street, W.

1871 DUKES, CLEMENT, M.D., B.S., Sunnyside, Rugby.

1877 DUNBAR, J. J. MACWHIRTER, M.D., Hedingham House, Clapham-common, S.W.

1889 DUNCAN, JOHN, M.D., St. Petersburg.

1884 DUNN, LOUIS ALBERT, M.B., M.S., The College, Guy's Hospital, S.E.

1879 DURHAM, FREDERIC, M.B., 52, Brook street, W.

1899 EASTES, GEORGE LESLIE, M.B., B.Sc., 35, Gloucester terrace, W.

1893 ECCLES, WILLIAM MCADAM, M.S., 124, Harley street, W.

1892 EDDOWES, ALFRED, M.D., 28, Wimpole street, W.

1880 **EDMUNDS**, WALTER, M.C., 2, Devonshire place, Portland place, W. (C. 1892-4.)

1882 EDWARDS, F. SWINFORD, 55, Harley street, W.

1889 ELAM, WILLIAM HENRY, New Barnet, Herts.

1883 ELDER, GEORGE, M.D., 17, Regent street, Nottingham.

1867 ELLIS, JAMES, M.D., Coburg street, Fratton, Portsmouth, and California.

1863 ENGELMANN, GEORGE JULIUS, M.D., A.M., 336, Beacon street, Boston, Mass., U.S.A.

1875 EVANS, JULIAN AUGUSTUS, A.M., M.D., 123, Finborough road, Redcliffe square, S.W.

1894 EVANS, WILLMOTT H., M.D., 13, Taviton street, Gordon square, W.C.

1879 EVE, FREDERIC S., 125, Harley street, W. (M.G.C. 1884-94. C. 1885-7. V.-P. 1895-7.)

1876 EWART, JAMES COSSAR, M.B., C.M., F.R.S., School of Medicine, Edinburgh.

1881 EWART, Sir JOSEPH, M.D., Bewcastle, Dyke road, Brighton.

1877 **EWART**, WILLIAM, M.D., 33, Curzon street, W. (C. 1889-91.)

1859 **Ewens**, JOHN, 17, Redland Grove, Bristol.

1887 EYLES, CHARLES HENRY, Gold Coast Colony.

1897 EYRE, JOHN W. H., M.D., Embankment Chambers, Villiers street, W.C.

1899 FAGGE, CHARLES H., M.S., 22, St. Thomas's street, S.E.

1889 FAIRBANK, FREDERICK ROYSTON, M.D., Hillside, Westcott, Dorking.

1894 FAWCETT, JOHN, M.D., 24, St. Thomas's street, S.E.

1872 FENN, EDWARD L., M.D., Grey Friars, Colchester.

1883 FENWICK, E. HURRY, 14, Savile row, W. (C. 1894-7.)

Elected

1872 FENWICK, JOHN C. J., M.D., Long Framlington, Morpeth.

1863 **FENWICK** SAMUEL, M.D., 29, Harley street, W.

1892 FENWICK, W. SOLTAU, M.D., 8, Devonshire street, W.

1885 FÉRÉ, CHARLES, M.D., Médecin de Bicêtre; Boulevard St. Michel 37, Paris.

1897 FISHER, THEODORE, M.D., 25, Pembroke road, Clifton, Bristol.

1882 FLEMING, GEORGE, C.B., LL.D., Higher Leigh, Combe Martin, North Devon.

1893 FLETCHER, H. MORLEY, M.A., M.D., B.C., 98, Harley street, W.

1872 FORBES, DANIEL MACKAY, 32, Oakfield road, West Croydon.

1866 **Foster,** Sir BALTHAZAR WALTER, M.D., M.P., 80, Grosvenor road, Westminster.

1872 FOTHERBY, HENRY I., M.D., Woodthorpe Cote, Reigate.

1891 FOULERTON, ALEXANDER GRANT RUSSELL, 15A, Porchester Gardens, Bayswater, W. (C. 1900—).

1880 FOWLER, JAMES KINGSTON, M.A., M.D., 35, Clarges street, W. (C. 1887-8.)

1878 FOX, THOMAS COLCOTT, B.A., M.B., 14, Harley street, W. (C. 1892-4.)

1896 FREYBERGER, LUDWIG, M.D., 41, Regent's park road, N.W.

1891 FRIPP, ALFRED DOWNING, M.S., 19, Portland place, W.

1864 FRODSHAM, JOHN MILL, M.D., Streatham, S.W.

1899 FÜRTH, KARL, M.D., 64, Harley street, W.

1894 FURNIVALL, PERCY, 28, Weymouth street, Portland place, W.

1893 FYFFE, WILLIAM KINGTON, M.B., 1, Boullcott street, Wellington, New Zealand.

1880 GABBETT, HENRY SINGER, M.D., 8, Chiswick place, Eastbourne.

1858 **Gairdner,** Sir WILLIAM TENNANT, K.C.B., M.D., LL.D.Edin., F.R.S., 225, St. Vincent street, Glasgow. (V.-P. 1891-2.)

1890 GALLOWAY, JAMES, M.A., M.D., 54, Harley street, W. (C. 1899—.)

1870 GALTON, JOHN H., M.D., Sylvan road, Upper Norwood, S.E.

1846 **GARROD,** Sir ALFRED BARING, M.D., F.R.S., 10, Harley street, W. (C. 1851. V.-P. 1863-5.)

1892 GARROD, ARCHIBALD EDWARD, M.D., 9, Chandos street, Cavendish square, W. (C. 1898—.)

1879 GARSTANG, THOMAS WALTER HARROPP, Headingley House, Knutsford, Cheshire.

1872 GARTON, WILLIAM, M.D., Inglewood, Aughton, near Ormskirk, Lancashire.

1880 GIBBES, HENEAGE, M.B., University of Michigan, Ann Arbor, Michigan, U.S.A.

1853 **GIBBON,** SEPTIMUS, M.D., 39, Oxford terrace, Hyde park, W.

1878 GIBBONS, ROBERT A., M.D., 29, Cadogan place, S.W.

1893 GIBBS, CHARLES, 115, Harley street, W.

1872 GILBART-SMITH, THOMAS, M.D., 68, Harley street, W.

1876 GILL, JOHN, M.D., 30, West mall, Clifton, Bristol.

1881 GLYNN, THOMAS ROBINSON, M.D., 62, Rodney street, Liverpool.

Elected

1898 Goadby, Kenneth Weldon, 6, Holly road, Cambridge park, Leytonstone, Essex.

1873 Godlee, Rickman John, M.B., M.S., 19, Wimpole street, W. (M.G.C. 1875-84. C. 1877-80, 1891-2. S. 1887-9. V.-P. 1893-4.)

1878 Golding-Bird, Cuthbert H., M.B., B.S., 12, Queen Anne street, W. (C. 1885-7. V.-P. 1894-6.)

1890 Goodall, E. Wilberforce, M.D., The Eastern Hospital, Homerton, N.E.

1871 Goodhart, James Frederic, M.D., 25, Portland place, W. (M.G.C. 1874-86. C. 1876-8, 1886-8. S. 1883-5. V.-P. 1892-3.)

1894 Gossage, Alfred Milne, M.B., B.Ch., 54, Upper Berkeley street, W.

1875 Gould, Alfred Pearce, M.S., 10, Queen Anne street, W. (C. 1883-5. V.-P. 1898-1900.)

1870 Gowers, Sir William, M.D., F.R.S., 50, Queen Anne street, W. (C. 1878-9. V.P. 1896-7.)

1888 Grant, J. Dundas, M.A., M.D., C.M., 8, Upper Wimpole street, W.

1900 Green, Alan B., M.A., M.B., B.C., Downing College, Cambridge.

1895 Green, Charles David, M.D., The Ferns, South street, Romford. (C. 1900—).

1867 Green, T. Henry, M.D., 74, Wimpole street, W. (M.G.C. 1869-83. C. 1871-3, 1878-9. S. 1875-6. V.-P. 1886-8.)

1873 Greenfield, William Smith, M.D., B.S., 7, Heriot row, Edinburgh. (M.G.C. 1874-81. C. 1877-80. V.-P. 1893-4.)

1886 Greves, Edwin Hyla, M.D., Rodney House, Suffolk road, Bournemouth.

1897 Griffith, John, 16, Harley street, W.

1887 Griffiths, Joseph, M.D., C.M., 63, Trumpington street, Cambridge.

1876 Griffiths, Thomas D., M.D., Hearne Lodge, Swansea.

1899 Grübb, R., M.D., 67, Wimpole street, W.

1887 Habershon, Samuel Herbert, M.D., 88, Harley street, W.

1851 **Hacon**, E. Dennis, 269, Mare street, Hackney, N.E. (C. 1872.)

1892 Hadley, Wilfred James, M.D., 58, Harley street, W.

1882 Haig, Alexander, M.D., 7, Brook street, W.

1899 Hall, Arthur J., M.B., 342, Glossop road, Sheffield.

1894 Hallidie, Andrew Hallidie Smith, M.B., 50, Noord street, Johannesburg.

1886 Hamilton, David James, M.B., 41, Queen's road, Aberdeen.

1890 Handfield-Jones, Montagu, M.D., 35, Cavendish square, W.

1886 Handford, Henry, M.D., 6, Regent street, Nottingham.

1891 Hankin, E. H., Agra, India.

1882 Harbinson, Alexander, M.D., County Lunatic Asylum, Lancaster.

1893 Harley, Vaughan, M.D., 25, Harley street, W.

1879 Harris, Vincent Dormer, M.D., 22, Queen Anne street, W.

1891 Haslam, William F., 54, Newhall street, Birmingham.

1870 Haward, John Warrington, 57, Green street, Grosvenor square, W. (C. 1879-81. V.-P. 1890-1.)

Elected

1899 HAWKES, CLAUDE SOMERVILLE, Frescati, Ann Street, Brisbane, Queensland, Australia.

1886 HAWKINS, FRANCIS HENRY, M.D., 73, London street, Reading.

1890 HAWKINS, HERBERT PENNELL, M.D., 56, Portland place, W. (C. 1898—.)

1856 **HEATH**, CHRISTOPHER, 36, Cavendish square, W. (C. 1866-7. V.-P. 1879-81.)

1892 HEATON, GEORGE, M.B., B.Ch., 33, Temple row, Birmingham.

1881 HEBB, RICHARD G., M.A., M.D., 9, Suffolk street, S.W. (M.G.C. 1891—. C. 1891-3. 1898—. S. 1896-7.)

1884 HEBBERT, CHARLES ALFRED, care of C. Baylor, 7, Water street, Boston, U.S.A.

1879 HENDERSON, GEORGE COURTENAY, M.D., Kingston, Jamaica, West Indies.

1869 HENSLEY, PHILIP J., M.D., 4, Henrietta street, W.

1884 HERRINGHAM, WILMOT PARKER, M.D., 13, Upper Wimpole street, W. (C. 1894-7.)

1892 HEWLETT, RICHARD TANNER, M.D., Jenner Institute of Preventive Medicine, Chelsea gardens, Grosvenor road, S.W.

1897 HICHENS, PEVERELL S., M.B., B.Ch., Hospital for Consumption, Brompton, S.W.

1880 HOBSON, JOHN MORRISON, M.D., Glendalough, Morland road, Croydon.

1854 **HOLMES**, TIMOTHY, 6, Sussex place, Hyde park, W. (C. 1862-3. S. 1864-7. C. 1868. V.-P. 1869-71.)

O.M. HOLTHOUSE, CARSTEN, 38, Townshend Terrace, Richmond, Surrey. (C. 1852-4. V.-P. 1874-5.)

1878 HOOD, DONALD WILLIAM CHARLES, M.D., 43, Green street, Park lane, W.

1864 HOOD, WHARTON P., M.D., 11, Seymour street, W.

1895 HOPKINS, FREDERICK GOWLAND, M.B., New Museums, Cambridge. (C. 1899—.)

1900 HORDER, THOMAS JEEVES, M.D., B.Sc., St. Bartholomew's Hospital, E.C.

1897 HORNE, WALTER J., M.B., 27, New Cavendish street, Portland place, W.

1879 HORROCKS, PETER, M.D., 45, Brook street, W.

1883 HORSLEY, VICTOR, M.B., B.S., F.R.S., 25, Cavendish square, W. (C. 1888-9. V.-P. 1900—.)

1896 HORTON-SMITH, PERCIVAL, M.D., B.C., 15, Upper Brook street, W.

1880 **HOVELL**, T. MARK, 105, Harley street, W.

1893 HOWARD, ROBERT JARED BLISS, M.D., 31, Queen Anne street, W.

1875 HOWSE, HENRY GREENWAY, M.S., 59, Brook street, W. (M.G.C. 1876-84. C. 1878-81.)

1856 **HUDSON**, JOHN, M.D., 11, Cork street, W.

1874 HUMPHREYS, HENRY, M.D., St. Mary Church road, Torquay.

1897 HUNT, E. L., c/o King, King, and Co., Bombay.

1897 HUNT, GEORGE B., M.D., 47, Albemarle crescent, Scarborough.

1888 HUNTER, WILLIAM, M.D., 103, Harley street, W. (C. 1897-1900.)

1852 **HUTCHINSON**, JONATHAN, F.R.S., 15, Cavendish square, W. (C. 1856-9. V.-P. 1872-3, 1881-3. P. 1879-80.)

1884 HUTTON, HENRY RICHMOND, M.B., 8A, St. John street, Manchester.

1880 INGRAM, ERNEST FORTESCUE, Newcastle, Natal, S. Africa.

Elected

1886 JACKSON, ARTHUR MOLYNEUX, M.D., Kent County Asylum, Barming Heath, Maidstone.

1865 JACKSON, J. HUGHLINGS, M.D., F.R.S., 3, Manchester square, W. (C. 1872-3. V.-P. 1888-9.)

1875 JALLAND, WILLIAM HAMERTON, St. Leonard's House, Museum street, York.

1897 JAMES, GEORGE T. B., Carlisle mansions, Victoria street, S.W.

1888 JAMES, JAMES THOMAS, M.D., 30, Harley street, W.

1853 **Jardine**, JOHN LEE, Capel, near Dorking, Surrey.

1897 **JENNER**, LOUIS, M.B., 4A, Bloomsbury square, W.C.

1881 JENNINGS, WILLIAM OSCAR, M.D., Rue Marbœuf, Avenue des Champs Elysées, Paris.

1866 JESSOP, THOMAS RICHARD, 31, Park square, Leeds.

1878 JOHNSON, ARTHUR JUKES, Yorkville, Ontario, Canada.

1876 JOHNSON, CHARLES HENRY, Winton House, Basingstoke, Hants.

1888 JOHNSON, RAYMOND, M.B., B.S., 11, Wimpole street, Cavendish square, W. (C. 1896-9.)

1854 JOHNSTONE, ATHOL A. W., St. Moritz House, 61, Dyke road, Brighton.

1899 JONAS, HERBERT C., Duxford, Cambridgeshire.

1853 **JONES**, SYDNEY, M.B., 18, Portland place, W. (C. 1864-6. V.-P. 1886-7.)

1888 JONES, TALFOURD, M.B., Eastbourne.

1862 **JONES**, THOMAS RIDGE, M.D., 4, Chesham place, S.W. (C. 1882-4.)

1886 JULER, HENRY EDWARD, 23, Cavendish square, W.

1898 KERR, ARTHUR CORRIE, M.D., M.C., 7, Lower Seymour street, W.

1867 KELLY, CHARLES, M.D., Ellesmere, Gratwicke road, Worthing, Sussex. (M G.C. 1872-4. C. 1874.)

1897 KELLY, CHARLES E. M., M.D., 9, Highbury Grove, N.

1879 KESTEVEN, WILLIAM HENRY, Hillwood, Waverley grove, Hendon, N.W.

1859 KIALLMARK, HENRY WALTER, 5, Pembridge gardens, W. (C. 1875-6.)

1882 KIDD, PERCY, M.D., 60, Brook street, W. (C. 1889-91.)

1867 KING, EDWIN HOLBOROW, 30, Norfolk square, Hyde park, W.

1871 KING, ROBERT, M.B., Boyfield House, Moulton, Spalding, Lincolnshire.

1852 **KINGDON**, J. ABERNETHY, Threadneedle street, E.C.

1888 KYNSEY, Sir WILLIAM RAYMOND, K.C.M.G., Oriental Club, Hanover square, W. [Travelling.]

1878 LANCEREAUX, ETIENNE, M.D., 44, Rue de la Bienfaisance, Paris.

1882 LANE, WILLIAM ARBUTHNOT, M.B., M.S., 21, Cavendish square, W. (C. 1891-3.)

1869 LARCHER, O., M.D.Par., 97, Rue de Passy, Paris. [M. Kliensieck, Libraire, Rue de Lille 11, Paris, per Messrs. Longmans.]

1884 LARDER, HERBERT, Whitechapel Infirmary, Vallance road, N.E.

1897 LATHAM, ARTHUR C., M.D., 44, Brook street, W.

1873 LATHAM, PETER WALLWORK, M.D., 17, Trumpington street, Cambridge.

1876 LAW, WILLIAM THOMAS, M.D., 5, Duchess street, Portland place, W.

Elected

1853 LAWRENCE, HENRY JOHN HUGHES, Picton House, Llandowror, St. Clears. (C. 1873-5.)

1892 LAWRENCE, THOMAS WILLIAM PELHAM, M.B., 64, South hill park, N.W.

1893 LAWSON, ARNOLD, M.D., 12, Harley street, W.

1859 LAWSON, GEORGE, 12, Harley street, W. (C. 1870-1. V.-P. 1884-5.)

1879 LAYCOCK, GEORGE LOCKWOOD, M.B., Melbourne, Victoria, Australia.

1891 LAZARUS-BARLOW, WALTER SYDNEY, M.D., Cecil House, Cavendish road, Sutton, Surrey.

1875 LEDIARD, HENRY AMBROSE, M.D., 35, Lowther street, Carlisle. (C. 1897-1900.)

1877 **LEES**, DAVID B., M.D., 22, Weymouth street. W. (C. 1890-2.)

1867 LEES, JOSEPH, M.D., 21, Brixton road, S.W.

1877 LEESON, JOHN RUDD, M.D., C.M., 6, Clifden road, Twickenham.

1868 LEGG, JOHN WICKHAM, M.D. (Travelling.) (C. 1874-5.)

1892 LEITH, ROBERT FRASER CALDIE, M.B., C.M., B.Sc.

1892 **Leudet**, ROBERT, 16, Rue du Contrat Social, Rouen, France.

1861 LICHTENBERG, GEORGE, M.D., 47, Finsbury square, E.C.

1897 LISTER, THOMAS DAVID, 95, Wimpole street, W.

1895 LITTLE, ERNEST GRAHAM GORDON, M.D., 61, Wimpole street, W.

1889 LITTLE, JOHN FLETCHER, M.B., 32, Harley street, W.

1862 **LITTLE**, LOUIS S., Shanghai, China.

1896 LITTLEWOOD, HARRY, 40, Park square, Leeds.

1874 LIVEING, EDWARD, M.D., 52, Queen Anne street, W.

1863 **LIVEING**, ROBERT, M.D., 11, Manchester square, W. (C. 1876.)

1881 LUBBOCK, MONTAGU, M.D., 19, Grosvenor street, W.

1897 LUCAS, ALBERT, 9, Easy row, Birmingham.

1873 LUCAS, R. CLEMENT, M.B., B.S., 50, Wimpole street, W. (C. 1883-5.)

1879 LUNN, JOHN REUBEN, St. Marylebone Infirmary; Rackham street, Ladbroke grove road, W. (C. 1897-1900.)

1887 LYON, THOMAS GLOVER, M.D., 1, Victoria street, S.W.

1871 **MAC CORMAC**, Sir WILLIAM, Bart., K.C.V.O., 13, Harley street, W. (C. 1878-80.)

1893 MCFADYEAN, JOHN, M.B., Royal Veterinary College, Great College street, N.W. (C. 1899—.)

1896 MACFADYEN, ALLAN, M.D., B.Sc., Jenner Institute of Preventive Medicine, Chelsea gardens, S.W. (C. 1900—).

1899 MCGAVIN, LAWRIE H., Guy's Hospital, S.E.

1882 MACKENZIE, FREDERIC MORELL, 29, Hans place, S.W.

1885 MACKENZIE, HECTOR WILLIAM GAVIN, M.A., M.D., 59, Welbeck street, W. (C. 1895-7.)

1870 MACKENZIE, JOHN T., Bombay, India.

1878 MACKENZIE, STEPHEN, M.D., 18, Cavendish square, W. (C. 1888-90.)

1879 MACLAGAN, THOMAS JOHN, M.D., 9, Cadogan place, S.W.

1865 MACLAURIN, HENRY NORMAND, M.D., 187, Macquarie street, Sydney, New South Wales.

Elected

1896 McWeeney, Edmond Joseph, M.D., M.Ch., 84, St. Stephen's green, Dublin.

1885 Maguire, Robert, M.D., 4, Seymour street, W.

1877 Makins, George Henry, 47, Charles street, Berkeley square, W. (C. 1889-91. V.-P. 1899—.)

1887 Malcolm, John David, M.B., C.M., 13, Portman street, W.

1892 Mann, Harold Edward, Alderney.

1890 Manson, Patrick, M.D., C.M., F.R.S., 21, Queen Anne street, W. (C. 1900—.)

1876 Maples, Reginald, Kingsclere, near Newbury.

1868 Marsh, F. Howard, 30, Bruton street, W. (C. 1876-7.) (V.-P. 1889-90.)

1887 Martin, Sidney, M.D., B.S., F.R.S., 10, Mansfield street, W. (C. 1893-6. V.-P. 1900—.)

1889 Mason, David James, M.D., Rosemont, Maidenhead.

1867 Mason, Philip Brookes, Burton-on-Trent.

1898 Masterman, Ernest William Gurney, 3, Newnham terrace, Cambridge.

1892 Masters, John Alfred, M.D., 31, Albert Gate, Hyde Park, S.W.

1884 Maudsley, Henry Care, M.D., 11, Spring street, Melbourne, Victoria.

1897 Maxwell, J. P., c/o E.P. Mission, Amoy, China.

1852 **MAY**, George, M.B., Reading.

1888 May, William Page, M.D., B.Sc., 9, Manchester square, W., and Helouan, near Cairo, Egypt (November to April).

1881 Maylard, Alfred Ernest, M.B., 4, Berkeley terrace, Glasgow.

1874 Meredith, William Appleton, C.M., 21, Manchester square, W.

1894 Michels, Ernst, M.D., 6, West street, Finsbury circus, E.C.

1882 Money, Angel, M.D., Hunter street, Sydney, New South Wales.

1899 Moore, Frederick Craven, M.D., The Priory, Ardwick Green, Manchester.

1879 Moore, Norman, M.D., 94, Gloucester place, Portman square, W. (C. 1885-7. M.G.C. 1889—. V.-P. 1895-7.)

1875 Morgan, John H., 68, Grosvenor street, W. (C. 1886-8.)

1874 Morison, Alexander, M.D., C.M., 14, Upper Berkeley street, W.

1869 **MORRIS**, Henry, M.A. (Trustee), 8, Cavendish square, W. (C. 1877-9, 1884-6. S. 1881-3. V.-P. 1888-9.)

1879 Morris, Malcolm Alexander, 8, Harley street, W.

1894 Morrice, George Gavin, M.D., Holy Trinity Vicarage, Weymouth.

1891 Morton, Charles A., 14, Vyvyan terrace, Clifton, Bristol.

1875 Morton, John, M.B., Guildford.

1884 Mott, Frederick Walker, M.D., F.R.S., 25, Nottingham place, W. (C. 1891-3. V.-P. 1899—.)

1900 Muir, Robert, M.D., 20, Hartington place, Edinburgh.

1893 Mummery, John Howard, 10, Cavendish place, W.

1876 Munro, William, M.D., C.M., 13, King William street, E.C.

1899 Murray, George R., M.D., 11, Ellison place, Newcastle-on-Tyne.

1885 Murray, Hubert Montague, M.D., 25, Manchester square, W. (C. 1896-9.)

Elected

1894 MURRAY, JOHN, M.B., B.Ch., 110, Harley street, W.

1887 NASON, EDWARD NOEL, M.D., 80, Abbey street, Nuneaton.
1873 NETTLESHIP, EDWARD, 5, Wimpole street, W. (C. 1882-4.)
1875 NEWBY, CHARLES HENRY, 15, Landport terrace, Southsea, Hants.
1884 NEWLAND-PEDLEY, FREDERICK, 32, Devonshire place, Portland place, W.
1865 NEWMAN, WILLIAM, M.D., Stamford, Lincolnshire.
1895 NIAS, J. BALDWIN, M.D., 5, Rosary gardens, S. Kensington, S.W.
1868 NICHOLLS, JAMES, M.D., Trekenning House, St. Columb, Cornwall.
1876 NICHOLSON, FRANK, M.D., 29, Albion street, Hull.
1864 **NORTON**, ARTHUR T., C.B., Ashampstead, Berks. (C. 1877-9.)
1883 NORVILL, FREDERIC HARVEY, M.B., Dibrooghur, India.
1856 NUNN, THOMAS WILLIAM, 8, Stratford place, W. (C. 1864-6. V.-P. 1878-80.)

1880 O'CONNOR, BERNARD, M.D., 25, Hamilton road, Ealing.
1873 O'FARRELL, Sir GEORGE PLUNKETT, M.D., 19, Fitzwilliam square, Dublin.
1894 OGLE, CYRIL, M.B., 96, Gloucester place, W. (C. 1899—.)
1876 OLIVER, JOHN FERENS, M.D., 12, Old Elvet, Durham.
1888 OPENSHAW, THOMAS HORROCKS, M.S., 16, Wimpole street, W.
1875 ORD, WILLIAM MILLER, M.D., The Hall, Salisbury (C. 1880-2. V.-P. 1893-4.)
1892 ORD, WILLIAM WALLIS, M.D., The Hall, Salisbury.
1879 ORMEROD, JOSEPH A., M.D., 25, Upper Wimpole street, W. (C. 1887-9.)
1875 **OSBORN**, SAMUEL, 1A, Devonshire street, W., and Maisonnette, Datchet, Bucks.
1881 OWEN, ISAMBARD, M.D., 40, Curzon street, W.
1865 OWLES, JAMES ALLDEN, M.D., Hill View, Woking, Surrey.

1884 PAGET, STEPHEN, 70, Harley street, W. (C. 1894-7.)
1895 PAKES, WALTER CHARLES, Guy's Hospital, S.E.
1897 PARFITT, CHARLES D., M.D., London, Canada.
1898 PARKER, ARTHUR PERCY, M.B., B.Ch., 27, Beaumont street, Oxford.
1872 PARKER, ROBERT WILLIAM, 13, Welbeck street, W. (C. 1881-3. M.G.C. 1884-94. V.-P. 1897-9.)
1874 PARKER, RUSHTON, M.B., B.S., 59, Rodney street, Liverpool.
1853 **PARKINSON**, GEORGE, Halsdown House, Exmouth, South Devon.
1882 PASTEUR, WILLIAM, M.D., 4, Chandos street, W. (C. 1893-6.)
1899 PATON, EDMUND PERCY, M.D., M.S., 84, Park street, Grosvenor square, W.
1885 PAUL, FRANK THOMAS, 38, Rodney street, Liverpool.
1865 **PAVY**, FREDERICK WILLIAM, M.D., LL.D., F.R.S., 35, Grosvenor street, W. (C. 1872-4. V.-P. 1891-2. P. 1893-4.)
1868 PAYNE, JOSEPH FRANK, M.D. (TRUSTEE), 78, Wimpole street, W. (M.G.C. 1872-85. C. 1873-5, 1883-5. S. 1880-2. V.-P. 1888-9. P. 1897-8.)

Elected

1872 PEARCE, JOSEPH CHANING, M.D., C.M., Montague House, St. Lawrence-on-Sea, Kent.
1879 PEEL, ROBERT, 130, Collins street East, Melbourne, Victoria.
1899 PEMBERY, MARCUS SEYMOUR, M.D., B.Ch., Guy's Hospital, S.E.
1889 PENBERTHY, JOHN, Royal Veterinary College, Camden Town, N.W.
1887 PENROSE, FRANCIS GEORGE, M.D., 84, Wimpole street, W.
1884 PEPPER, AUGUSTUS JOSEPH, M.B., C.M., 13, Wimpole street, W.
1900 PERKINS, JOSEPH JOHN, M.B., 41, Wimpole street, Cavendish square, W.
1899 PERNET GEORGE, 77, Upper Gloucester place, N.W.
1888 PERRY, EDWIN COOPER, M.D., Superintendent's House, Guy's Hospital, S.E.
1878 PHILIPPS, SUTHERLAND REES, M.D., St. Ann's heath, Virginia Water, Chertsey.
1878 PHILLIPS, JOHN WALTER, 30, Stanley street West, Melbourne, Victoria.
1863 PICK, THOMAS PICKERING, 18, Portman street, W. (M.G.C. 1869-73. C. 1870-1. V.-P. 1885-7.)
1896 PIGG, T. STRANGEWAYS, New Museums, Cambridge.
1893 PINKERTON, ROBERT A., M.A., M.D., 15, South Norwood hill, S.E.
1884 PITT, GEORGE NEWTON, M.D., 15, Portland place, W. (M.G.C. 1889-97. C. 1890-2, 1896-9. S. 1894-6. V.-P. 1899—.)
1876 PITTS, BERNARD, M.A., M.C., 109, Harley street, W. (C. 1888-90.)
1899 PLIMMER, HENRY GEORGE, 28, St. John's Wood road, N.W.
1883 POLAND, JOHN, 2, Mansfield street, Cavendish square, W.
1882 POLLARD, BILTON, M.B., B.S., 24, Harley street, W. (C. 1895-7.)
1850 POLLOCK, JAMES EDWARD, M.D., 52, Upper Brook street, W. (C. 1862-4. V.-P. 1879-81.)
1870 POORE, GEORGE VIVIAN, M.D., 32, Wimpole street, W. (C. 1883-5.)
1879 **POTTER**, HENRY PERCY, M.D., St. Mary Abbotts Infirmary, Marloes road, Kensington, W.
1884 POWER, D'ARCY, M.A., M.B., 10A, Chandos street, W. (C. 1891-3. 1899—. M.G.C. 1897—. S. 1897-9.)
1865 POWER, HENRY, 37A, Great Cumberland place, W. (C. 1876-7.)
1887 PRATT, WILLIAM SUTTON, M.D., Penrhos House, Rugby.
1884 PRICE, JOHN A. P., M.D., 124, Castle street, Reading.
1888 PRIMROSE, ALEXANDER, M.B., C.M., 196, Simcoe street, Toronto, Canada.
1882 PRINGLE, JOHN J., M.B., C.M., 23, Lower Seymour street, W.
1895 PURVIS, WILLIAM PRIOR, M.D., 2, Avenue place, Southampton.
1865 PYE-SMITH, PHILIP HENRY, M.D., F.R.S., 48, Brook street, W. (C. 1874-7. V.-P. 1890-1.)

1897 RANKIN, GUTHRIE, M.D., 4, Chesham street, S.W.
1890 **Ransom**, WILLIAM BRAMWELL, M.D., The Pavement, Nottingham.
1891 RATCLIFFE, JOSEPH RILEY, M.B., C.M., Wake green, Moseley.
1887 RAVEN, THOMAS FRANCIS, Broadstairs, Kent.
1870 RAY, EDWARD REYNOLDS, 67, Grosvenor street, W.
1875 REID, ROBERT WILLIAM, M.D., C.M., 8, Queen's gardens, Aberdeen
1881 RENNER, WILLIAM, Wilberforce street, Free Town, Sierra Leone.

Elected

1893 RENNIE, GEORGE EDWARD, M.D., College street, Hyde park, Sydney, N.S.W.
1899 RICHMOND, BENJAMIN ARTHUR, M.B., B.S., B.Sc., Guy's Hospital, S.E.
1895 RITCHIE, JAMES, M.D., 28, Beaumont street, Oxford.
1865 **Roberts**, DAVID LLOYD, M.D., 11, St. John's street, Manchester.
1871 ROBERTS, FREDERICK THOMAS, M.D., 102, Harley street, W. (C. 1883-5.)
1878 ROBERTS, WILLIAM HOWLAND, M.D., Surgeon, Madras Army.
1888 ROBERTSON, ROBERT, M.D., The Bungalow, Ventnor, Isle of Wight.
1885 ROBINSON, ARTHUR HENRY, M.D., Mile End Infirmary, Bancroft road, N.E.
1882 ROBINSON, TOM, M.D., 9, Princes street, Cavendish square, W.
1897 ROGER-SMITH, HUGH, M.D., 1, College terrace, Fitzjohn's avenue, N.W.
1888 ROLLESTON, HUMPHRY DAVY, M.A., M.D. 55, Upper Brook street, Grosvenor square, W. (C. 1894-7. 1900—. M.G.C. 1895—. S. 1898-1900.)
1858 **ROSE**, HENRY COOPER, M.D., 16, Warwick road, Maida hill, N.W. (C. 1873-4.)
1876 ROSE, WILLIAM, M.B., B.S., 17, Harley street, W.
1875 ROSSITER, GEORGE FREDERICK, M.B., Cairo Lodge, Weston-super-Mare.
1877 **ROTH**, BERNARD, 38, Harley street, W., and "Wayside," 1, Preston park avenue, Brighton.
1888 ROUGHTON, EDMUND WILKINSON, M.D., 38, Queen Anne street, W.
1891 ROUILLARD, LAURENT ANTOINE JOHN, M.B., Durban, Natal.
1899 ROWLANDS, ROBERT P., Guy's Hospital, S.E.
1891 RÜFFER, MARC ARMAND, M.D., The Quarantine Board, Alexandria.
1897 RUNDLE, HENRY, 13, Clarance parade, Southsea.
1895 RUSSELL, JAMES SAMUEL RISIEN, M.D., 4, Queen Anne street, W.
1891 RUSSELL, WILLIAM, M.D., 3, Walker street, Edinburgh.

1854 SANDERSON, Sir JOHN BURDON, Bart., M.D., D.C.L., F.R.S., 64, Banbury road, Oxford. (M.G.C. 1869-76. C. 1864-7. V.-P. 1873-4.)
1897 SANTI, PHILIP R. W. DE, 15, Stratford place, W.
1886 SAUNDBY, ROBERT, M.D., 83A, Edmund street, Birmingham.
1871 SAUNDERS, CHARLES EDWARD, M.D., Sussex County Lunatic Asylum, Hayward's Heath.
1890 SAUNDERS, FREDERICK WILLIAM, M.B., B.C., Chieveley House, Newbury.
1873 SAVAGE, GEORGE HENRY, M.D., 3, Henrietta street, Cavendish square, W. (C. 1881-3.)
1882 SAVILL, THOMAS DIXON, M.D., 60, Upper Berkeley street, W.
1891 SCHORSTEIN, GUSTAVE ISIDORE, M.B., B.Ch., 11, Portland place, W.
1899 SELIGMANN, CHARLES G., St. Thomas's Hospital, S.E.
1877 SEMON, Sir FELIX, M.D., 39, Wimpole street, W. (C. 1885-7.)
1894 SEQUEIRA, JAMES HARRY, M.D., 13, Welbeck street, Cavendish square, W.
1872 SERGEANT, EDWARD, D.P.H., Lancashire County Council, Public Health Department, County Offices, Preston.
1876 SHARKEY, SEYMOUR J., M.D., 22, Harley street, W. (M.G.C. 1884-95 C. 1884-6. V.-P. 1895-7.)

Elected

1880 SHATTOCK, SAMUEL G., 4, Crescent road, The Downs, Wimbledon, S.W. (M.G.C. 1884—. C. 1885-7, 1893-6. S. 1890-2. V.-P. 1896-8. E. 1900.)

1898 SHAW, HAROLD BATTY, M.D., University College Hospital, Gower street, W.C.

1885 SHAW, LAURISTON ELGIE, M.D., 64, Harley street, W.

1886 **SHERRINGTON**, CHARLES SCOTT, M.D., F.R.S., University College, Liverpool. (C. 1894-7.)

1856 **SHILLITOE**, BUXTON, 2, Frederick's place, E.C.

1875 SIDDALL, JOSEPH BOWER, M.D., C.M., Conybeare, Northam, Bideford.

1880 SILCOCK, A. QUARRY, M.D., B.S., 52, Harley street, W. (C. 1888-90.)

1866 SIMS, FRANCIS MANLEY BOLDERO, 12, Hertford street, W.

1892 SLATER, CHARLES, M.B., St. George's Hospital, S.W.

1887 SMALLPEICE, WILLIAM DONALD, 42, Queen Anne's gate, S.W.

1875 **Smee**, ALFRED HUTCHINSON, The Grange, Hackbridge, Carshalton, Surrey.

1879 SMITH, E. NOBLE, 24, Queen Anne street, W.

1887 SMITH, FREDERICK JOHN, M.D., 138, Harley street, W.

1875 SMITH, GEORGE JOHN MALCOLM, M.D., Hurstpierpoint, Sussex.

1894 SMITH, GUY BELLINGHAM, M.B., B.S., 24, St. Thomas's street, S.E.

1900 SMITH, J. LORRAIN, M.D., Queen's College, Belfast.

1873 SMITH, RICHARD T., M.D., 117, Haverstock hill, N.W.

1883 SMITH, ROBERT PERCY, M.D., 36, Queen Anne street, W.

1869 SMITH, ROBERT SHINGLETON, M.D., Deepholm, Clifton Park, Bristol.

1892 SMITH, SOLOMON CHARLES, M.D., Four Oaks, Walton-on-Thames, Surrey.

1856 SMITH, Sir THOMAS, Bart., 5, Stratford place, W. (C. 1867-9. V.-P. 1877-8.)

1866 SMITH, WILLIAM, Melbourne, Australia.

1870 SMITH, WILLIAM JOHNSON, Seamen's Hospital, Greenwich, S.E. (C. 1879-81.)

1870 SNOW, WILLIAM VICARY, M.D., Richmond Gardens, Bournemouth.

1888 SOLLY, ERNEST, M.B., Strathlea, Harrogate, Yorks.

1887 SPENCER, WALTER GEORGE, M.S., 35, Brook street, W. (M.G.C. 1894—C. 1896-9.)

1899 SPRIGGS, EDMUND IVENS, M.D., 26, St. Thomas's street, S.E.

1861 SQUIRE, ALEXANDER BALMANNO, M.B., 24, Weymouth street, W.

1890 STABB, EWEN CARTHEW, 57, Queen Anne street, W.

1895 STARLING, ERNEST HENRY, M.D., F.R.S., 8, Park square West, Regent's Park, N.W.

1896 STEPHENS, J. W. W., M.D., Pathological Laboratory, Cambridge.

1899 STEWARD, FRANCIS J., M.S., 24, St. Thomas's street, S.E.

1900 STEWART, PURVES, M.D., 133, Harley street, W.

1891 STILES, HAROLD JALLAND, M.B., C.M., 5, Castle terrace, Edinburgh.

1897 STILL, GEORGE F., M.D., 46, Gower street, W.C.

1879 STIRLING, EDWARD CHARLES, C.M.G., M.D., F.R.S., Adelaide, South Australia [care of Messrs. Elder & Co., 7, St. Helen's place, E.C.].

1883 STOKER, GEORGE, 14, Hertford street, W.

1884 STONHAM, CHARLES, 4, Harley street, W. (C. 1893-6.)

1875 STURGE, W. A., M.D., 29, Boulevard Dubouchage, Nice.

Elected

1871 **SUTHERLAND**, HENRY, M.D., 21, New Cavendish street, W.

1867 SWAIN, WILLIAM PAUL, 17, The Crescent, Plymouth.

1881 SYMONDS, CHARTERS JAMES, M.S., 58, Portland place, W. (M.G.C. 1884-91. C. 1886-8. V.-P. 1899—.)

1886 TARGETT, JAMES HENRY, M.B., M.S., 6, St. Thomas's street, S.E. (M.G.C. 1894—. C. 1894-5, 1897-1900. V.-P. 1900—. S. 1895-7.)

1870 TAY, WARREN, 4, Finsbury square, E.C. (C. 1881-2.)

1871 **TAYLOR**, FREDERICK, M.D., 20, Wimpole street, W. (M.G.C. 1879-89. C. 1879-81. V.-P. 1897-9.)

1885 TAYLOR, HENRY H., 10, Brunswick place, Brighton.

1892 TAYLOR, JAMES, M.D., 49, Welbeck street, W.

1879 THIN, GEORGE, M.D., 63, Harley street, W. (C. 1889-90.)

1852 **THOMPSON**, Sir HENRY, Bart., 35, Wimpole street, W. (S. 1859-63. C. 1865-7. V.-P. 1868-70.)

1897 THOMSON, H. CAMPBELL, M.D., 34, Queen Anne street, W.

1891 THOMSON, HENRY ALEXIS, M.D., 32, Rutland square, Edinburgh.

1884 THOMSON, JOHN, M.D., C.M., 14, Coates crescent, Edinburgh.

1894 THOMSON, STCLAIR, M.D., 28, Queen Anne street, W.

1892 **Thorburn**, WILLIAM, B.S., 2, St. Peter's square, and Rusholme Lodge, Rusholme, Manchester.

1874 THORNTON, JOHN KNOWSLEY, M.B., Hildersham Hall, Cambridge.

1872 THORNTON, WILLIAM PUGIN, 35, St. George's place, Canterbury.

1900 THURSFIELD, HUGH, M.D., 10, Bentinck street, W.

1880 TIBARD, NESTOR ISIDORE, M.D., 74, Harley street, W.

1884 TIVY, WILLIAM JAMES, 8, Lansdowne place, Clifton, Bristol.

1897 TOOGOOD, F. SHERMAN, M.D., The Infirmary, 282, High street, Lewisham, S.E.

1882 TOOTH, HOWARD HENRY, M.D., 34, Harley street, W. (C. 1892-4. M.G.C. 1895—.)

1886 TOTSUKA, KANKAI, Tokio.

1872 **TOWNSEND**, THOMAS SUTTON, 68, Queen's gate, S.W.

1899 TREDGOLD, ALFRED F., London County Asylum, Woodford Bridge, Essex.

1888 TREVELYAN, EDMOND F., M.D., 40, Park square, Leeds.

1881 TREVES, FREDERICK, 6, Wimpole street, W. (C. 1887-90. V.-P. 1895-7.)

1851 TROTTER, JOHN W., 4, St. Peter's terrace, York. (C. 1865-9.)

1895 TROUTBECK, HENRY, M.B., B.C., 148, Ashley gardens, S.W.

1859 **TRUMAN**, EDWIN THOMAS, 23, Old Burlington street, W.

1888 TUBBY, ALFRED HERBERT, M.S., 25, Weymouth street, Portland place, W.

1867 TUCKWELL, HENRY MATTHEWS, M.D., 64, High street, Oxford.

1858 TUDOR, JOHN, Dorchester, Dorset.

1882 TURNER, GEORGE ROBERTSON, 41, Half Moon street, W.

1863 TURNER, JAMES SMITH, 12, George street, Hanover square, W.

1890 TURNER, WILLIAM ALDREN, M.D., 13, Queen Anne street, W.

1893 TURNEY, HORACE GEORGE, M.D., M.Ch., 68, Portland place, W.

1858 **TURTLE**, FREDERICK, M.D., Kirkmead, Woodford, Essex.

1880 TYSON, WILLIAM JOSEPH, M.D., 10, Langhorne gardens, Folkestone.

Elected

1867 VENNING, EDGCOMBE, 30, Cadogan place, S.W.

1889 VOELCKER, ARTHUR FRANCIS, M.D., B.S., 31, Harley street, W. (C. 1895-7.)

1867 **WAGSTAFFE**, WILLIAM WARWICK, B.A., Purleigh, St. John's hill, Sevenoaks. (C. 1874, 1878-80. M.G.C. 1874-82. S. 1875-7.)

1885 WAKLEY, THOMAS, jun., 5, Queen's gate, S.W.

1893 WALKER, NORMAN PURVIS, M.D., 7, Manor place, Edinburgh.

1881 WALLER, BRYAN CHARLES, M.D., Masongill House, Cowan bridge, Kirkby-Lonsdale.

1890 WALLIS, FREDERICK CHARLES, M.B., B.C., 26, Welbeck street, W. (C. 1898—.)

1888 WALSHAM, HUGH, M.A., M.D., B.C., 114, Harley street, W.

1873 **WALSHAM**, WILLIAM JOHNSON, M.B., C.M., 77, Harley street, W. (C. 1881-3.)

1859 WALTERS, JOHN, M.B., Reigate, Surrey.

1892 WARD, ALLAN OGIER, M.D.Edin., Lansdowne House, Tottenham.

1892 WARING, HOLBURT JACOB, M.B., M.S., 9, Upper Wimpole street, W.

1889 WASHBOURN, JOHN WICHENFORD, M.D., 6, Cavendish place, W. (C. 1897—1900.)

1891 WATERHOUSE, HERBERT FURNIVALL, M.D., C.M., 81, Wimpole street, W.

1892 WEAVER, FREDERICK POYNTON, M.D., Cedar Lawn, Hampstead Heath, N.W.

1890 WEBB, CHARLES FREER, M.D., New street House, Basingstoke.

1894 **WEBER**, FREDERICK PARKES, M.D., 19, Harley street, W.

1858 **WEBER**, Sir HERMANN, M.D., 10, Grosvenor street, W. (C. 1867-70. V.-P. 1878-80.)

1864 WELCH, THOMAS DAVIES, M.D. (Travelling).

1894 WELLS, SYDNEY RUSSELL, M.D., 24, Somerset street, Portman square, W.

1892 WESBROOK, FRANK F., M.D.(Winnipeg).

1877 WEST, SAMUEL, M.D., 15, Wimpole street, W. (C.1884-6, 1891-3. S. 1889-90. V.-P. 1896-7.)

1888 WETHERED, FRANK J., M.D., 83, Harley street, W.

1891 WHEATON, SAMUEL WALTON, M.D., 76, The Chase, Clapham Common, S.W.

1867 WHIPHAM, THOMAS TILLYER, M.D., 11, Grosvenor street, W. (C. 1880-2.)

1869 WHIPPLE, JOHN H. C., M.D., Royal Army Medical Corps.

1877 WHITE, CHARLES HAYDON, 20, Shakespeare street, Nottingham.

1894 WHITE, CHARLES POWELL, M.B., 2, Blansford Gardens, Woodhouse Lane, Leeds.

1891 WHITE, GILBERT B. MOWER, M.B., B.S., 112, Harley street, W.

1881 WHITE, WILLIAM HALE, M.D., 65, Harley street, W. (C. 1888-90.)

1886 WHITE, WILLIAM HENRY, M.D., 43, Weymouth street, W.

1868 **Whitehead**, WALTER, 17, Market street, Manchester.

1897 WHITFIELD, ARTHUR, M.D., 12, Upper Berkeley street, Portman square, W.

Elected

1877 WHITMORE, WILLIAM TICKLE, 7, Arlington street, S.W.

1870 WICKSTEED, FRANCIS WILLIAM, 2, Prince's mansions, Victoria street, S.W.

1869 WILKIN, JOHN F., M.D., M.C., Rose Ash House, South Molton, N. Devon.

1871 WILKINSON, J. SEBASTIAN, The Laurels, Oakengates, Salop.

1879 WILLCOCKS, FREDERICK, M.D., 14, Mandeville place, W.

1886 WILLETT, EDGAR, M.B., 25, Welbeck street, W. (C. 1897—1900.)

1869 WILLIAMS, ALBERT, M.D. (Travelling).

1858 **Williams**, CHARLES, 48, Prince of Wales road, Norwich.

1866 WILLIAMS, CHARLES THEODORE, M.D., 2, Upper Brook street, W. (C. 1875-8.)

1881 WILLIAMS, DAWSON, M.D., B.S., 101, Harley street, W. (C.1893-6.)

1872 WILLIAMS, Sir JOHN, Bart., M.D., 63, Brook street, W. (C. 1878-80.)

1881 WILLIAMS, W. ROGER, Beaufort House, Clifton Down, Clifton.

1876 WILLIAMSON, JAMES MANN, M.D., Ventnor, Isle of Wight.

1900 WILLIAMSON, OLIVER K., M.B., B.C., 170, Sewardstone road, Victoria Park, E.

1863 WILLIS, FRANCIS, M.D., Asheville, N. Carolina, U.S.A.

1889 WILSON, ALBERT, M.D., Leytonstone, Essex.

1888 WILSON, CLAUDE, M.D., C.M., Church road, Tunbridge Wells.

1859 WILSON, EDWARD THOMAS, M.B., Montpelier terrace, Cheltenham.

1891 WILSON, THEODORE STACEY, M.D., C.M., 29, Temple row, Birmingham.

1861 **Windsor**, THOMAS, Medical Library, Boston, Mass., U.S. [care of B. F. Stevens, 4, Trafalgar square, W.].

1889 WINGRAVE, V. HAROLD WYATT, 11, Devonshire street, Portland place, W.

1874 WISEMAN, JOHN GREAVES, Dearden street, Ossett, Yorkshire.

1865 WITHERBY, WILLIAM H., M.D., Pitt place, Coombe, Croydon.

1883 WOODCOCK, JOHN ROSTRON, Abberley, near Stourport, Worcestershire.

1883 WOODHEAD, GERMAN SIMS, M.D., 6, Scrope terrace, Cambridge. (C. 1891-3. V.-P. 1898—1900. M.G.C. 1899—.)

1879 WOODWARD, G. P. M., M.D., Deputy Surgeon General; Sydney, New South Wales.

1884 WORTS, EDWIN, 6, Trinity street, Colchester.

1869 WYMAN, WILLIAM S., M.D., Red Brae, 18, Putney hill, S.W.

1890 WYNNE, EDWARD T., M.B., Gladstone, Queensland.

1884 WYNTER, WALTER ESSEX, M.D., 30, Upper Berkeley street, W.

1872 YOUNG, HENRY, M.B., Monte Video, South America.

ANNUAL REPORT OF COUNCIL,

1899—1900,

PRESENTED AT THE ANNUAL MEETING, MAY 29TH, 1900.

YOUR Council have to report the election of thirty-six new members during the last session.

On the Council's nomination, the Society has elected to the honorary membership Sir Samuel Wilks, M.D., F.R.S., President of the Society in 1881–2; Prof. v. Recklinghausen, of Strassburg; and Dr. P. P. E. Roux, Sub-director of the Pasteur Institute, Paris.

There have been seven resignations, and seven losses by death.

The actual number of members is 681, of whom thirteen are honorary members, 384 resident and 284 non-resident.

The death-roll this year includes Sir James Paget, Bart., F.R.S., Dr. F. C. Turner, Mr. W. Adams, Mr. B. E. Brodhurst, Mr. J. N. C. Davies-Colley, and Sir W. O. Priestley.

Sir James Paget was President of the Society in 1887–8.

Dr. F. C. Turner was Secretary in 1891–3, and Senior Vice-President at the time of his death. His contributions to the 'Transactions' were numerous and valuable.

Mr. W. Adams was one of the last surviving original members of the Society, and was a Vice-President in 1867–9. Mr. Davies-Colley was a Vice-President in 1890–91.

A change has been made in the meetings of the Society with the object of increasing the scope and interest of the communications. Laboratory Meetings have been held at the Jenner Institute, University and King's Colleges, and at the laboratories of the Royal Colleges of Physicians and Surgeons.

The Society is under a debt of gratitude to Dr. Allan Macfadyen, to Professor Sidney Martin, Professor Edgar Crookshank, and

Dr. T. G. Brodie for their hospitality at these Laboratory Meetings.

Professor Sims Woodhead has kindly invited the Society to meet in the Pathological Laboratory at Cambridge on June 30th, 1900, and the Council has accepted his offer on behalf of the Society.

To encourage discussion and expression of opinion at these Meetings the Council passed the following resolution:

"That the discussions held at Laboratory Meetings should not be reported in the medical journals, and that abstracts of the papers read should only be published if the authors desired it and handed in abstracts."

During the past session the following debates have taken place:

"On the pathological unity of tabes and general paralysis," Nov. 21st, Dec. 5th, Dec. 19th, 1899.

"On the proteids in the urine," Feb. 20th, March 20th, 1900.

"On the blood in disease," April 3rd, May 1st, 1900.

The Council have decided—

(i) That the 'Transactions' be published in four or five parts, and in a single volume at the end of the year, and that members shall have their choice in which form the 'Transactions' shall be sent to them.

(ii) That in addition to the Publication Committee an editor be appointed, who shall be *ex officio* a member of the Council. The editor shall be elected biennially, and be eligible for re-election.

The Council elected Mr. Shattock, editor.

The following alterations in the Bye-laws were passed at a general meeting of the Society held on December 19th, 1899:

The omission of the following Bye-laws:

XXXIII. "They (the Secretaries) shall be responsible for the editing of the 'Transactions.'"

XLIV. "They (the Council) shall, at a special meeting or meetings after the close of the Session, determine what communications and illustrations shall be published in the 'Transactions.'"

LV. "In the remarks made in reference to specimens exhibited, all discussions on abstract points shall be as far as possible avoided; and the topics of dia-

gnosis and treatment shall not be introduced farther than is necessary to illustrate the pathology of the subject."

The insertion after the word "May," in Bye-law LII, of the words "except the first Tuesday in January, and Easter Tuesday."

Bye-law LII. The Ordinary Meetings of the Society shall be held on the First and Third Tuesday in each month, from the Third Tuesday in October to the Third Tuesday in May, at Half-past Eight p.m. precisely.

The insertion after the word "Treasurer," in Bye-law V, of the words "an Editor."

Bye-law V. The Officers of the Society shall be elected from the members, and shall consist of a President, four or more Vice-Presidents, a Treasurer, and two Secretaries, who, with twenty other members and the Trustees, shall constitute the Council, and shall have the management of the Society's affairs.

The insertion of the following Bye-laws :

OF THE EDITOR.

XXXIX. That the Editor be responsible for the editing of the Society's 'Transactions' in such manner as the Council shall direct.

XL. That he be *ex officio* a member of the Council.

XLI. That he be elected biennially, and be eligible for re-election.

XLII. That he receive an honorarium annually at the discretion of the Council.

The index to vols. 39—50, prepared by Mr. Shattock, is near its completion, and it is anticipated will be in the hands of members of the Society during the present year.

The Council passed the following resolution on January 16th, 1900 :

"That a paper may be published in any part of the 'Transactions' before the date at which it is read, or may be published without being read at all, should the exigencies of time make the latter necessary.

> Such communications shall be placed on the *agenda* and announced at one of the Society's meetings; and, the meeting approving, may then be published before being read, or without being read should the time at disposal during the session be too limited to allow of this."

During the absence of the President, Mr. W. W. Cheyne, F.R.S., in South Africa, the chair has been taken by Mr. A. Pearce Gould, to whom the Council and the Society are deeply indebted for the time and care he has devoted to the Society's welfare.

Financial statement by the Treasurer.

Owing to the gratifying accession of new members the financial position of the Society is somewhat better than it was a year ago; and, in spite of the fact that the new method of publication of the 'Transactions' will probably add to the annual expenditure, it is confidently hoped that this may be met without trenching upon capital funds.

Compared with the accounts of the Session 1898–9, the current Session shows an increase in income of £68 5*s*. 3*d*., whilst on the expenditure side there is an increase of £25 16*s*. 4*d*., giving a net excess of income over expenditure of £41 7*s*. 9*d*. The total cost of publication of Vol. L of the 'Transactions' amounted to £246 10*s*. 3*d*.

The balance in hand (£144 19*s*. 2*d*.) includes the accumulated capital of £66 5*s*. derived from Life Composition Fees received during the past five years.

During the coming Session the Society will have to bear the cost of publication of the General Index—an item of extraordinary expenditure, which will require to be defrayed out of capital; and the Council have therefore authorised the Trustees to sell out sufficient stock to meet this exceptional draft on the Society's funds.

The Stock now held by the Society amounts to £1114 3*s*. 2*d*. invested in Consols.

THE PATHOLOGICAL SOCIETY OF LONDON.

Statement of Receipts and Payments from 10th May, 1899, to 15th May, 1900.

RECEIPTS.

	£	s.	d.	£	s.	d.
Balance at Bank—10th May, 1899	106	12	9			
,, in hand—Petty Cash, &c.	4	3	11			
				110	16	8
342 Subscriptions at £1 1s.	359	2	0			
25 Entrance Fees	26	5	0			
11 ,, Non-Resident	34	13	0			
3 Composition Fees	15	15	0			
1 ,, Fee for 'Transactions'	10	10	0			
				446	5	0
Sale of Transactions:						
Publisher	38	14	3			
Per Adlard's	4	2	6			
				42	16	9
Dividends on Consols				29	12	4
				£629	10	9

PAYMENTS.

	£	s.	d.	£	s.	d.
Meetings:						
Expenses of Rooms to Christmas, 1899	105	0	0			
Refreshments, Attendance, &c.	26	15	0			
Expenses of Meeting, Laboratory, University College	2	5	0			
Microscopes (Session 1898–9)	18	1	6			
Dickinson: Reporting Meetings	4	14	6			
				156	16	0
Transactions:						
Printing, Binding, &c., of Vol. L	177	3	11			
Illustrations for Vol. L	66	3	4			
,, Vol. LI	6	10	2			
Index to Vol. L	3	3	0			
				253	0	5
Secretariat and Treasury:						
General Printing and Stationery	27	1	4			
Council Notices	2	0	0			
Secretarial Assistance	15	15	0			
Mr. Clarke for Attendance	5	5	0			
,, for Collection of Subscriptions	15	15	0			
				65	16	4
Petty Cash Expenditure				8	18	2
Bank Charges				0	0	8
Balance at Bank	143	1	5			
Petty Cash in hand	1	17	9			
				144	19	2
				£629	10	9

NOTE.—The sum of £1114 8*s.* 2*d.* is invested in Consols.

Audited and found correct, May 15th, 1900.

SIDNEY COUPLAND, *Treasurer.*

H. D. ROLLESTON, C. A. BALLANCE, *Hon. Secretaries.*

FRANCIS C. ABBOTT, H. MORLEY FLETCHER, *Auditors.*

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PRESIDENT'S ADDRESS.

GENTLEMEN,—In taking this chair for the first time allow me to thank you most heartily for the high honour you have done me in electing me to the presidency of this, the leading Pathological Society in this country. I can assure you that I feel this honour most deeply; but I must at the same time confess that it is with the greatest anxiety that I take up the position, knowing the difficulty of following in the footsteps of the long roll of distinguished men who have already occupied this chair. As, however, you have deemed me worthy of it, I can only do my best and crave your indulgence for my shortcomings.

Three days hence it will be exactly fifty-three years ago that this Society met for the first time, and during these years it has done a great work in increasing our knowledge of the changes which occur in the body as the result of disease. When the Society was founded, the subject of Pathology was practically conterminous with a study of the morbid changes in the tissues as seen by the naked eye; pathological histology had hardly begun. Hence, the functions of the Society, as then defined, were—"The exhibition and description of specimens, drawings, microscopical preparations, casts or models of morbid parts," and exhibitors were specially enjoined to avoid discussions on abstract points as far as possible. Since that time the aim of this Society has been to collect facts both as to the naked-eye morbid anatomy, and also, *pari passu* with the development of histology, as to the microscopical characters of the diseased tissues. In carrying out the aim thus set before it, this Society has

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been eminently successful, and our 'Transactions' are a perfect mine of knowledge with regard to all departments of morbid anatomy. The encouragement thus given to the study of morbid anatomy has led to the accumulation of an enormous number of facts, and the ordinary changes as observable by the naked eye have now been pretty exhaustively worked out; while much has also been done as regards the coarser histological characters of the affected tissues. Indeed, as regards what may be called the rougher details of morbid anatomy, the number of absolutely new facts which remain to be added is probably comparatively few, and those which are likely to be met with are rather varieties of distribution and site of well-known lesions than entirely new lesions, and are for the most part of clinical rather than of pathological interest.

But while pathology has been thus advancing as regards morbid anatomy, it has also been opening out in many other directions, which in some ways promise to be more fruitful than morbid anatomy as regards the ultimate aim of pathological work, namely, the arrest or cure of disease. It is difficult for us to realise what a change has taken place in the science of pathology since this Society was founded. At that time pathological histology was in its very infancy, experimental and chemical pathology had hardly begun, and bacteriology was unknown. Nowadays, on the other hand, pathologists are turning their attention more and more to the elucidation by observation and experiment of the causes which lead to the first deviations from the normal, and the modes in which lesions already known are brought about; in other words, the chief work of pathologists at the present time is in the direction of experimental pathology. Already much light has been thrown on the intimate nature of pathological processes by these researches, and the harvest to be reaped from them promises to be very great.

Perhaps the most striking of the recent developments of pathological research is the birth and rapid growth of bacteriology. Even twenty years ago bacteriology as a science was practically non-existent; and although at that time the Listerian principles as applied to the treatment of wounds were already established, they were founded rather on accurate observation and closely reasoned theoretical considerations than

on definitely proved bacteriological facts as to the particular kinds of micro-organisms associated with septic diseases and the modes in which they act. Since that time, however, discoveries have followed one another in rapid succession, definitely proving the causal relation between micro-parasites and various diseases. That of itself is a notable achievement in the short time that has elapsed since this study commenced; but the science has already progressed far beyond that stage. Investigators have not remained content with demonstrating the causes of infective diseases, but they have extended their studies to the various conditions under which the causal agents act, the mode in which they produce disease, the relation of the tissues of the body to the invading parasites, and the microscopical and chemical changes which take place; indeed, the researches have gone still further, and some of the results obtained have already been successfully applied in the prevention and cure of disease.

These advances in bacteriology have also greatly influenced other departments of pathology. The facts thus made out have already thrown light on a variety of other morbid processes, and have led to research as to the mode in which deviations from the normal, other than those caused by parasites, originate, and in which the gross changes already known from the study of morbid anatomy come into being. In fact, while on the one hand morbid anatomy has been advancing to the position of a more or less exact science, the attention of pathologists has become more and more concentrated on the cause of those changes and the mode in which they are brought about; and pathology no longer consists of morbid anatomy and pathological histology, but includes ætiology, bacteriology, experimental pathology, and pathological chemistry.

If we try to form an estimate of the value, on the one hand, of morbid anatomy, and, on the other, of experimental pathology, under which we may for the sake of brevity include bacteriology and pathological chemistry, we must look at the matter from the point of view of the relation of pathology to clinical work; for we must always bear in mind that the ultimate aim of pathology, as of other departments of medical research, is the discovery of facts which may be of value in the cure or arrest of disease. On one point there can, I think, be no dispute, and that is that morbid anatomy is the foundation

stone of pathology; and just as a knowledge of anatomy is essential to the student of the normal body, so a knowledge of morbid anatomy is essential to the student of pathology. And as regards its application to medical and surgical practice, the gain which has resulted from the advanced state of knowledge of morbid anatomy is undoubtedly very great, although it is nevertheless distinctly limited. This gain may be looked at from a twofold point of view; namely, from that of diagnosis and prognosis, and from that of cure.

On the one hand, the more accurate our knowledge of the changes which occur in disease and of the course which they follow, the more definitely are we able to picture to ourselves the exact state of matters in any given case, and to forecast the future; in other words, the greater our knowledge of morbid anatomy the more accurate will be our diagnosis and prognosis. Indeed, many of our most accurate diagnosticians have received their early training to a great extent at this Society.

On the other hand, from the point of view of the cure of the patient, the gain from morbid anatomy falls chiefly to the department of the surgeon. Morbid anatomy has, in fact, done a great deal to bring surgery to its present advanced position, more especially by showing the real extent of the morbid processes, and thus enabling the surgeon to operate intelligently and efficiently. In this respect I need only instance the improved results now obtained after operations for malignant disease, and also the more methodical and less destructive modes of operation for tuberculous lesions, both of which have resulted from the knowledge gained by morbid anatomy and histology. I believe, also, that the more advanced condition of morbid anatomy, as compared with experimental pathology, is one of the reasons why the surgeon is trenching more and more on the province of the physician.

From the point of view of the *cure of disease*, as contrasted with the cure of the patient, however, the gain to the physician from morbid anatomy alone is comparatively slight. It is true that the more exact knowledge of the state of matters now possessed enables the physician to relieve symptoms and aid nature to an extent which was not possible formerly; but till the mode in which the morbid changes come about, and the ultimate causes of the trouble and the way in which they act have

been made out, he can hardly hope to interfere actively and successfully in the way of bringing about a cure. And yet the ideal of medical practice must be not merely to aid nature to overcome the disease, but by active intervention to arrest its progress, to lead to a retrogression of the morbid changes which have already occurred, and to eradicate the causes of these changes. For however efficient surgery may be in many cases in relieving the patient or in ridding him of his disease, it must be admitted that it is often a very severe and it may be an imperfect measure. Indeed, the treatment of disease at the present time is very much on a par with the methods in vogue a century ago in the treatment of crime. At that time the essential remedy was to get rid of the criminal altogether, while but little was done to eradicate the causes of crime; and the result was that crime remained as active as ever. So at the present time with surgery as applied to many diseases. By surgery we ruthlessly extirpate the diseased parts, and while by so doing we may rid the particular patient of his disease, we do so at the expense of healthy tissues, and often of the patient's strength, and we do nothing against the causes of disease in general, and thus disease remains as active as ever. But just as at the present time the tendency is to try to reform the criminal and not to get rid of him, and at the same time to remove the causes of crime, such as ignorance, poverty, and so forth, so the ideal aim in the treatment of disease is to try to arrest its development, to bring about retrogression of the morbid process, and to root out its cause. This is, I believe, more likely to result from the study of the causes and mode of production of the morbid changes than by limiting our attention to these changes themselves; in other words, it is probable that more will be, so to speak, "got out" of experimental pathology in the way of cure of disease than out of morbid anatomy.

That this is so is shown, to take one example alone, by the results already obtained by the practical application of bacteriological discoveries as to ætiology, the protective arrangements of the body, artificial immunity, and so forth. As the result of the advances in ætiology, very effectual measures are now being elaborated for stamping out or limiting the spread of a variety of infective diseases, such as cholera, plague, tuberculosis, malaria etc.; while from the study of artificial immunity useful

results have already accrued, not only in the way of protection, but also of cure, or at least modification of the course of diseases,—for example, in diphtheria, plague, tetanus, etc. Even where success has not yet been obtained the promise is great. Most of us will remember the wonderful effects produced by Koch's first tuberculin,—how the visible disease seemed to melt away and disappear in the course of a few days. If only the effects produced in the first instance had been permanent what an enormous advance it would have been, and how much better for the patient than our present means of treating tuberculous lesions by surgical measures, or even by reclining on deck-chairs in the open air! Nevertheless, although the attempt did not prove a success, it showed that the dream of causing the retrogression of morbid processes is not a wild one; and even in the instance of tuberculosis it does not seem too much to hope that, as the result of the marvellous additions which are being daily made to our knowledge in the department of bacteriology, the expectations excited by Koch's researches may after all be realised. If, indeed, we could only find out the explanation of how it is that a simple laparotomy in a case of tuberculous peritonitis often leads to marked improvement, and not unfrequently to complete disappearance of the disease and of the morbid changes produced by it, we would already be far on the way to realise this hope.

It follows from what has been said that, whether viewed from the point of view of pathological interest, or from that of practical importance, no society which calls itself a Pathological Society can afford to retain its constitution as originally fixed when pathology only meant morbid anatomy, but must extend its borders so as to include all recent developments. On the one hand, the foundation of pathology, namely, morbid anatomy, must not be neglected, and everything calculated to strengthen that foundation must be encouraged. But, on the other hand, the edifices which are being erected on that foundation, grouped together under the head of experimental pathology, must also be carefully tended, and due proportion and every encouragement given to work in that direction.

It is well to ask from time to time in the case of any society whether it has done and is doing its duty in keeping up with the advances of medical science. That this Society has in former

years been too backward in recognising the value of speculation and experiment cannot, I fear, be denied. Up till a few years ago the original functions of the Society were undoubtedly too rigidly adhered to, and in the early days of bacteriology and experimental pathology workers were not only not encouraged, but were actually discouraged, from bringing their work before this Society. Indeed, in the early days of bacteriology, it was almost impossible to bring work before the notice of the profession except by publication in the medical journals. This naturally gave rise to great discontent among workers at experimental pathology, which increased in degree as the number of these workers multiplied. But, although tardily, the necessity of widening the bounds of this Society was at length recognised, and in the revised rules of 1893 we find that in describing the functions of this Society there were added to the original definition, which I have already quoted, the words,—"and also by the communication of chemical, experimental, and other researches or observations relating to the nature and results of disease and by discussions thereon." By this extension in the functions of the Society it has been thrown freely open to all departments of pathological research, and it was to be hoped that full advantage would be taken of it. Nevertheless, if we look at the recent volume of our 'Transactions,' we find that though there is a distinct increase in the amount of experimental work, it still does not occupy the position it ought, having regard to its interest and importance; and the meetings still retain to a great extent their old character. Indeed, it is pretty well known that we are at the present time face to face with the possibility that the more active workers in experimental pathology may break off from this Society entirely, and form special societies for the study of the special branches of pathology in which they are interested.

Such a result as the formation of special societies dealing with the different branches of pathology would be very lamentable and disastrous both to this Society and to the workers themselves,—the more lamentable as at the present time it is quite unnecessary. The time has certainly not yet arrived, if, indeed, it ever will, when such a separation would be either safe or advisable. No doubt at the present time, when pathological science is advancing so rapidly and branching out in so

many directions, a certain amount of specialism in work is unavoidable; but just as in medicine, so in pathology, it is an evil, and should be restricted as far as possible. I freely admit that life is too short to enable any one man to keep in the forefront of all departments of medical science, or even of pathology itself; but a knowledge, even though superficial, of what is being done in branches other than that in which the individual worker is himself interested is better than none. It may enable the investigator to take a more correct view of the meaning of his own observations, and may also give him ideas which may be applied to his own work. How can he better or more easily acquire a knowledge of what is being done than by giving up the short time necessary to attend the meetings of this Society, and thus hearing and seeing what is going on in all departments? A further advantage to the worker is that by bringing the results of his researches to a general society his methods and conclusions may be criticised, not only by those working on the same lines, but by others who can look at them from a different point of view. At the same time, also, errors into which he may have fallen from insufficient knowledge of other departments of pathology may be corrected. It is, for example, quite possible that an investigator, not thoroughly familiar with morbid anatomy, may take an erroneous view of some lesion which he has observed or even produced,—an error which would, no doubt, be very speedily corrected at this Society.

There is another point of view which emphasises the desirability of keeping this Society a general society, and encouraging in every way we can communications on all topics. The function of a society of this kind is not limited to the reception and discussion of work; but it is also in part educational for the profession at large. I daresay many of our members are not themselves actively engaged in pathological work, and come here with the view of keeping up their knowledge, of hearing the latest views, and, if possible, of applying what they see and hear to practice. Were the subject split up among a number of different societies, such a man could not find time to attend them all, and would thus be deprived of the opportunity of keeping up his knowledge, and it may be of improving the practice of his profession. From all these considerations it will, I think, be evident that whether we regard

the advantage of the Society itself, of the workers, of pathology, or of the profession at large, it is our duty to do all in our power to attract pathological work of all kinds to this Society, and to preserve a due proportion between the different directions of pathological research.

We have lately tried to find out from those actively engaged in experimental work how it is that more advantage is not taken of this Society, why the formation of other societies is thought desirable, and what we can do to meet their views and prevent this unfortunate occurrence. The following seem to be the chief points:

In the first place, the fact that the basis of this Society was widened in 1893 does not seem to be sufficiently widely known; or, if known, the idea seems still to be prevalent that experimental work is not acceptable here. I hope in future that it will be thoroughly understood that this Society is open for all pathological work, whatsoever direction it takes, and I feel sure that any experimental work which is brought here will be most acceptable and highly appreciated.

In the second place, many who are studying special branches, such as bacteriology, do not like to have their papers sandwiched in between others on subjects in which they are not specially interested. In this, I think, for the reasons aforesaid, they make a mistake. It is, however, merely a question of the arrangement of business to have cognate subjects brought forward on the same evening; indeed, the attempt to do so has always been made by our secretaries. We propose, however, to arrange still further, so that on different evenings different departments shall have the first place. For example, on one evening bacteriological work could be taken first, and if not sufficient to fill the evening, papers on other subjects could follow; on a second evening papers on morbid anatomy would have the first place; on a third evening papers on experimental pathology, and so on. In this way those interested only in special subjects would know that on a particular evening these subjects would come first, and they would not need to sit through a whole meeting till the matter in which they were interested was reached, and perhaps find that it was after all postponed till a subsequent occasion.

A third point which has been raised, and one on which much

stress is laid, is that it may be desirable from time to time to show living animals which have been experimented on and which present points of interest; and, further, that in the case of experiments requiring elaborate apparatus, cultivations which would lose their characters by shaking, and so on, it is not always easy or possible to transport them here. As regards the first point, it is perhaps not very advisable that these premises should be licensed; and, besides, they do not belong to us. Both these difficulties can, however, be readily overcome by arranging for some of our meetings to be held in the larger laboratories. Tentatively the Council has accepted four such invitations for this session, which are announced on the cards; and should these arrangements prove a success, the number might, if necessary, be still further extended in future. From these laboratory meetings we hope that much advantage will accrue, both to this Society and to every one concerned. By means of them the members of the Society will be brought more closely into contact with laboratory work than can be the case in this room; while conversely it is to be hoped that they will lead those engaged in research work to take a greater interest in this Society.

Another reason assigned for withholding work from this Society is the delay in the publication of the 'Transactions.' This has, however, been already met to some extent by granting permission to authors to publish their papers in the 'Journal of Pathology' before the 'Transactions' appear. Whether anything can be done in the way of still further meeting this objection is a matter which is at present engaging the attention of the Council.

I hope it will not be thought that in thus advancing the claims of experimental pathology for special consideration, and in advocating the adoption of any measures which will keep those working at pathology in one society, I desire to alter too much or too suddenly the character of this Society, or to discourage in any way what has up till now been its chief work, namely, the study of morbid anatomy and histology. There is in reality plenty of room for all, and I only want not to give undue prominence to one part of pathology at the expense of others.

In connection with the exhibition of morbid specimens, how-

ever, I must say that I should like to see Rule 55 deleted from our rules, more especially that part of it which says,—"In the remarks made in reference to specimens exhibited all discussions on abstract topics shall be as far as possible avoided." This limitation was, no doubt, quite right at the time that this Society was founded, and when a sufficient number of facts had not yet been collected on which to found satisfactory speculations. Now, however, plenty of facts have been accumulated, we may, I think, with advantage reason with regard to them, and I should like to see the description of morbid specimens accompanied as far as possible by some speculation, however crude or erroneous, as to causation, mode of production, relation to other lesions, and so forth. We may go on collecting facts *ad infinitum;* if we do not attempt to generalise or draw conclusions from these facts, we do not in reality advance the science of pathology. The simple exhibition of specimens is merely making our minds receptacles for facts, while an hypothesis, however imperfect, founded on those facts makes us think and incites further discussion and investigation with the view of proving or disproving it. Nor must we draw the line too closely in excluding the effects of treatment, and more especially symptoms, provided, of course, that they throw light on the pathological process. In the case of the nervous system in particular, the interest and value of a specimen would in many cases be greatly enhanced if accompanied by some sketch of the symptoms and secondary changes associated with it.

I fear I have trespassed too much on your time. My only excuse is my desire for the welfare of this Society. Pathology is the groundwork of practical medicine and surgery, and, till a sound pathology is arrived at, our attempts to cure disease must be imperfect and more or less guess-work. There can be no higher work than that of aiding in building up the foundation of sound therapeutics and practice, and the value of a society of this kind in encouraging investigation and in sifting the wheat from the chaff cannot be over-estimated. May it long live and prosper!

REPORT.

SESSION 1899–1900.

1. *A diphtheria-like organism found in pigeons.*

By A. Macfadyen, M.D., and R. T. Hewlett, M.D.

A swabbing was sent up in the usual way to the Jenner Institute by Dr. Sharman, of Rickmansworth, to be examined for the presence of the diphtheria bacillus. The report sent to him stated that the Klebs-Loeffler bacillus had been found. Dr. Sharman then informed us that the swabbing had been taken from the throat of a pigeon, suffering from a disease known as "pigeon canker." This interesting fact led us to follow up the matter, and for this purpose we obtained a number of diseased birds. These presented a variety of lesions,—(*a*) in the form of a scab on the scalp, (*b*) as a warty growth about the eyelids, (*c*) as a large growth attached to the maxilla, (*d*) as a membrane on the palate. Whether all these lesions are one and the same disease, modified by position and other circumstances, we are not prepared to say, but undoubtedly the maxillary tumour will reproduce the warty growth on the eyelids on inoculation. The warty growth on the eyelid is about the size of a pea, but may enlarge and close the eye, and afterwards drop off, leaving the subjacent tissues quite healthy. Microscopically it has the structure of molluscum. The maxillary lesion may become as large as a small nut, presenting in appearance a yellowish, dryish, and caseous mass. On the palate the membrane is very firmly adherent. In all these phases of the disease we found the diphtheria-like organism in numbers, and usually mixed with cocci. The bacilli

presented the Klebs-Loeffler appearance as regards size, parallel arrangement, and polar staining. The bacilli were non-motile, and stained by Gram's method. We have obtained apparently two strains: No. 1 giving a dry and adherent growth on serum like the xerosis bacillus, and also a pellicle on broth like the Parke diphtheria bacillus; and No. 2 more closely resembling in growth, etc., the diphtheria bacillus as usually met with. The first strain was obtained from the scab, and gave a feeble indol reaction; the second was obtained from the throat, and gave a good indol reaction. Both strains produced acid like the diphtheria bacillus. We show cultures and microscopic specimens in illustration of the similarities between these organisms and the Klebs-Loeffler bacillus. The organisms further stain by Neisser's method. The disease can be inoculated directly from pigeon to pigeon, but we have hitherto failed in reproducing the disease in any of its phases in pigeons with pure cultures of the above bacillus. In guinea-pigs and mice solid and fluid cultures have given negative results as regards infection or intoxication.

It occurred to us to examine the throats of healthy pigeons, and in every case examined we have found the "throat" strain of the organism just described—that is, the one most closely resembling the Klebs-Loeffler bacillus. We will reserve any discussion of the ætiology and pathology of the disease for a future communication.

The point we wish to bring before the Society this evening is the interesting fact that in the throats of pigeons, *whether diseased or healthy*, there is to be found an organism which might be, and has by us been, mistaken for the Klebs-Loeffler bacillus, and which resembles it in morphological, cultural, and staining peculiarities—in everything, in short, save its pathogenic and toxic properties.

Since the above communication was made, Mr. Shattock has reminded us of his paper on "Molluscum contagiosum in Birds" in a previous volume of the 'Pathological Transactions' (vol. xlix, p. 394), and his descriptions of the disease agree very closely with what we have ourselves observed in these pigeons.

November 7th, 1899.

2. *The standardisation of anti-pneumococcic serum.*

By J. W. Eyre, M.D., and J. W. Washbourn, M.D.

Drs. J. W. Eyre and J. W. Washbourn gave a demonstration of the method adopted by them for standardising anti-pneumococcic serum. The method consisted in ascertaining how many fatal doses of living pneumococci one cubic centimetre of serum would protect against. The serum was injected into one of the veins of the ear of rabbits, and immediately afterwards the cultivation was injected into the peritoneal cavity. The cultivations were made upon blood-agar, and were of a constant virulence, which was maintained by repeated passages. The minimal fatal dose was ascertained by making an emulsion of a loopful (the same loop being used in all the experiments) of the cultivation in ten cubic centimetres of broth. Dilutions of this emulsion were made in broth, and thus any required fraction of a loopful could be obtained. The cultivation formed a perfect emulsion in which the cocci were evenly distributed; this accounted for the accuracy of the method.

The anti-pneumococcic serum differed from the anti-streptococcic in being much more powerful, and in the accuracy with which it could be standardised. The serum supplied by Dr. Pane, of Naples, protected against some three thousand fatal doses. Like the anti-streptococcic serum, it did not protect against all varieties of the pneumococcus. The authors had tested it against five varieties, and found that it protected perfectly against four, but had no effect upon the fifth. *November 7th*, 1899.

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3. *Problems of diphtheria immunity.*

By George Dean.

The questions treated of in this paper are connected with the process of immunisation of animals, the duration of active immunity and of antitoxin production, the loss of the power of

producing antitoxin in quantities of practical value, and the possibility of recovering that lost power.

The considerations involved in the solution of these problems are of considerable importance on both the theoretical and the practical sides. The experiments have been carried out on the horses employed at the Antitoxin Department of the Jenner Institute.

Salomonsen and Madsen[1] showed that the "marche ondulatoire" of immunisation described by Ehrlich and Brieger[2] in the case of tetanus immunisation also occurred in the case of diphtheria.

In Chart 1, after Salomonsen and Madsen, the injection of a large volume of toxin is seen to be followed by a fall in the antitoxin curve from 120 to 50 units per c.c., the lowest point in the curve being on the third day after the injection. This fall they assert is greater than can be accounted for by the amount of toxin neutralising the antitoxin present in the body, and they suggest that it is due to a paralysing influence of the toxin on the antitoxin-producing cells. From the third day the antitoxin curve rises, reaching its maximum about the ninth or tenth day, at which time it is higher than it was before the injection. The curve then begins to fall.

These writers suggest that the best time for bleeding an animal is the tenth day after the last injection. I believe this to be a most valuable observation and suggestion, and it is in entire accordance with the experience at Sudbury. They also suggest that it is the best time for giving a fresh injection of toxin. This seems to be a fair inference to draw from the observation, but I believe it is fallacious, and it is certainly opposed to my experience.

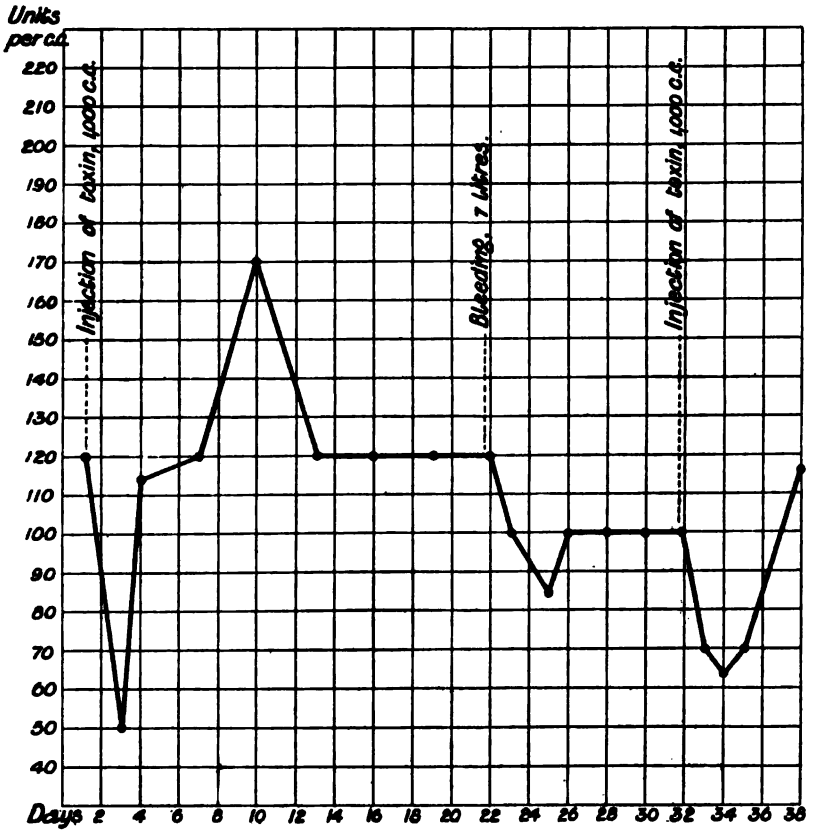
The best results, *i. e.* the most rapid immunisation and the highest antitoxin value, have been obtained by taking the time which corresponds to the lowest point of their antitoxin curve for giving a fresh injection, namely, from the second to the fourth day, most frequently the third day after the last injection. It is difficult to give an explanation of this on theoretical grounds, but regarding the practical results there can be no question.

[1] Salomonsen and Madsen, "Recherches sur la Marche de l'Immunisation active contre la Diphthérie," 'Annales de l'Institut Pasteur,' t. xi, No. 4, 1897, p. 315.

[2] Ehrlich und Brieger, "Beiträge zur Kenntniss der Milch immunisirter Thiere," 'Zeitschr. f. Hygiene,' xiii, 1893, S. 336.

By using this method of injecting the toxin on the second, third, or fourth day whenever it is possible—that is, when the animal will support the treatment, and as a rule there is little

CHART 1.



difficulty when the quantity of toxin is properly regulated—one obtains higher antitoxin values than by the method suggested by Madsen and Salomonsen. This result, too, can be attained—a matter of prime importance—in one half to one third of the time taken by their method.

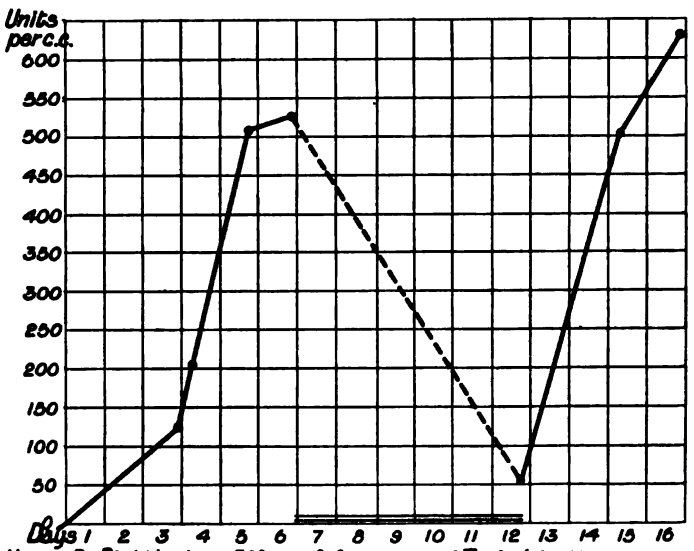
For example, by using this method, in one animal an antitoxic value of 400 to 500 units per c.c. was reached in two months, and on the third month of treatment the antitoxin of this animal reached a value of 850 to 900 units per c.c. As is well known to all workers at this subject, horses under the same treatment

vary greatly as to the strength of the antitoxin which they are capable of producing, but that the above result was not due to a mere variation is shown by the fact that several animals treated by the same method have given antitoxin approaching this in value.

All the tests of sera mentioned in this paper were carried out by Ehrlich's [1] newer method, and in the particular case mentioned he kindly controlled the testing. I desire here to express to him my warmest thanks for much help most generously given in connection with this subject.

What is the result of ceasing the injections of diphtheria toxin in an animal whose serum has reached a high antitoxin value? The opportunity of examining into this point occurred in a horse whose antitoxin contained about 530 units per c.c. Five

CHART 2.



Horse B. Diphtheria. Effect of Cessation of Toxin Injections on Antitoxin Curve.

months after the injections had ceased, the antitoxin had fallen to about 100 units per c.c. (see Chart 2).

In the case of active immunity the fall in antitoxin value has

[1] Ehrlich, "Die Wertbemessung des Diphtherieheilserums und deren theoretische Grundlagen," 'Abdruck aus dem klin. Jahrbuch,' 1897.

generally been thought to be much slower than in passive immunity. Recently, however, Behring[1] and Ransom[2] have stated that if the serum injected in the case of the passive immunity is taken from the same species of animal, the antitoxin is retained in the body as long as if it had been produced by the animal.

The above experiment tends to the conclusion that in the case of active diphtheria immunity, where the antitoxic value of the serum is high the fall is comparatively slow when the toxin injections are stopped. Whether the rate of fall is proportionate to the amount of antitoxin present in the blood cannot as yet be stated. Such an idea was suggested by Ehrlich in the case of passive immunity. I propose to carry out a series of comparative observations on this subject as the opportunity occurs.

At the end of five months the injections of toxin were recommenced, and the serum rapidly attained a strength of 600 antitoxin units per c.c.

A frequent course, perhaps the commonest, of the antitoxin curve in diphtheria is shown on Chart 3. As the treatment proceeds the value of the antitoxin improves for a few months, then with slight fluctuations remains stationary for a period. This period varies greatly in different animals. In some cases it may be only a few months. During this time the injections of toxin are continued between the bleedings. As shown by Salomonsen and Madsen,[3] there is then a tendency for a fall to occur in spite of repeated injections of toxin. This may take place, as will be seen later, when there is no question of the animal having been over-bled.

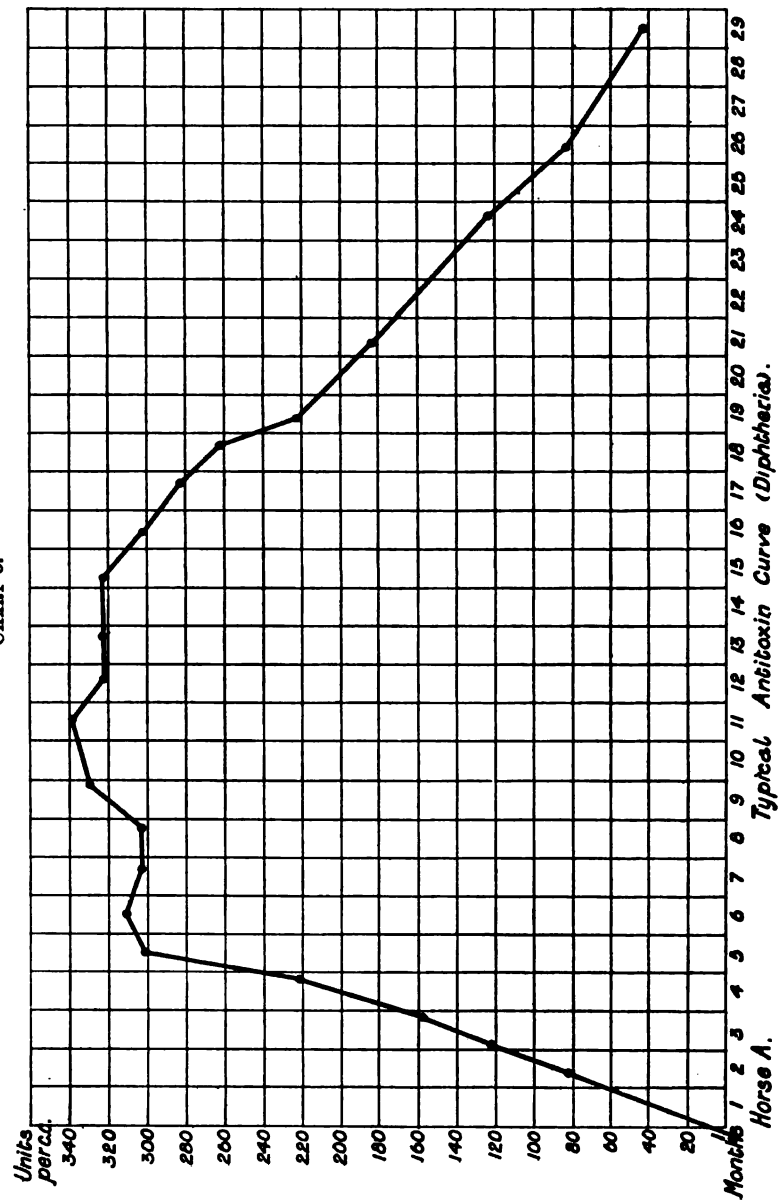
There are great variations in regard to the toleration of the toxin by different horses, both at the beginning of the immunisation and even after that has proceeded for some time. We had a striking example of that recently at Sudbury. Three horses of about the same size each received 1 c.c. of a particular toxin. Two of the animals were little affected by the dose, whereas the

[1] Behring, 'Allg. Therapie des Infectionskrankheiten,' 1899, p. 997.

[2] Ransom, "The Conditions which influence the Duration of Passive Immunity," 'Journ. of Path. and Bact.,' vol. vi, 1899, p. 180.

[3] Salomonsen and Madsen, "Undersögelser over Immunitet og Praedisposition. Kgl. Danske," 'Videnskabernes Selskaps Forhandlinger,' 1898, and 'Nord. med. Arkiv.,' Festband für Axel Key; ref. Weigert.

CHART 3.


Units per cc.
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
Months 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Horse A.
Typical Antitoxin Curve (Diphtheria).

third became severely ill with all the symptoms of toxæmia, and died in five days.

Of the hypersensitiveness in animals at the time when they are producing large quantities of antitoxin, described by Behring[1] in tetanus, I have not seen an example in the case of diphtheria.

When the curve is beginning to fall the injections of toxin do not have a greater effect. A horse at this stage of its immunisation may tolerate huge doses of toxin without being affected. It appears, therefore, to be approaching the condition of a naturally immune animal.

Why does the diminution of antitoxin production in diphtheria immunisation occur? Of the processes which give rise to it we have no definite knowledge. Weigert,[2] in a review of Erhlich's Seitenketten theory, attempts to give an explanation of it in accordance with that hypothesis. He says: "If a damaged cell shall not only regenerate part of itself, but shall also produce new parts in excess, the regenerating part of the cell, *i. e.* the central group, must above all itself remain uninjured. He therefore attributes this phenomenon of the fall in the antitoxin curve to damage done to the reparative part of the cell. According to this view such a loss must be irreparable. Reference to this will be made at a later part of the paper.

In connection with this fall in the antitoxin curve certain interesting questions arise.

The first question is, if such an animal, which has been highly immunised, "hyperimmunised," which has produced antitoxin of high value for a time, and which has lost that power of producing large quantities of protective substances, is left without treatment of any sort, *does the fall proceed so far that the animal's serum reaches a point where it has as little antitoxin as a normal horse's serum? Within what time does such a fall occur?*

I have had the opportunity of testing the serum of three horses which had been immunised against diphtheria, had produced antitoxin fit for therapeutic purposes, and whose antitoxin had fallen below a useful value. They had been struck off the diphtheria list and used for other purposes. One

[1] Behring, 'Allg. Therapie des Infectionskrankheiten,' 1899, p. 997.

[2] Weigert, "Einige neuere Arbeiten zur Theorie der Antitoxinimmunität," 'Ergebnisse der allg. Pathologie, u. s. w.,' Lubarsch u. Ostertag, iv J., 1897, S. 107.

had received no injection for three years, had not been bled, and had been used for outdoor work.

The second for three years had received no diphtheria toxin, but numerous injections of living cultures of streptococcus, and had been bled more than his total volume of blood.

The third had been off the diphtheria list for two years, and had received injections of urinary extracts. The animal had been frequently bled.

It is improbable that in the last two animals the injections could have had any influence on the question at issue.

Now on testing the serum of these animals in all these instances more antitoxin was present than in the serum of a normal animal. A number of observers, Roux and Martin,[1] Meade Bolton,[2] Cobbett,[3] and others, have shown that antitoxin may be present in the serum of normal horses. With the view of accurately comparing the serum of these three animals with normal horse serum I have examined the serum of fifteen normal horses, and I find that where antitoxin could be demonstrated to be present, its value could be expressed as a fraction of 1 unit per c.c., whereas the serum of these three horses had all an antitoxic value of at least from 1 to 5 units per c.c.

In addition to this, two out of the three animals which were tested by injections of toxin showed greater resistance than any normal horse I have seen.

Another question arises in connection with the fall in the antitoxin curve, viz. *whether those animals which at an earlier date had lost the power of producing antitoxin in useful quantities can recover that power, whether they can be actively immunised, and whether antitoxin of sufficient strength for therapeutical purposes can be obtained from them?*

Two of the animals already referred to were used for testing these points.

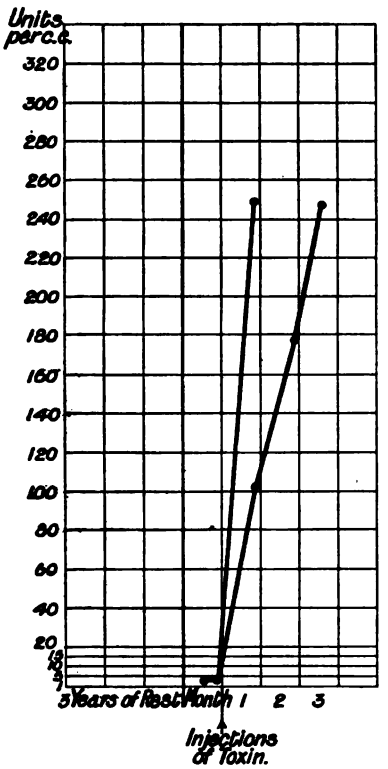
The first animal had been uninjected for three years. Dr. Bulloch tells me that, after a useful period, in spite of large doses of toxin the antitoxin value of its serum was found to be too low to be of any practical value.

[1] Roux and Martin, 'Annales de l'Institut Pasteur,' t. viii, 1894, p. 615.
[2] Meade Bolton, 'Journal of Exper. Med.,' vol. i, p. 543.
[3] Cobbett, 'Journ. of Pathology and Bacteriology,' 1894, p. 328.

After a series of injections very rapidly carried out during a month, the maximum single dose of toxin being 1000 c.c. D.T.N. 1, the animal's serum had altered to an antitoxic value of between 200 and 300 units per c.c.

In Chart 4 is shown the rapid rise of the curve compared with that of a fresh horse treated on parallel lines.

CHART 4.



Rise of Antitoxin Curve of Horses C, T & K, compared.

In the case of the second animal experimented on, a complete history of the immunisation was available. Chart 5 shows the history of the original immunisation, which was carried out by Dr. Bulloch. At that stage the period of high antitoxic value was brief, and in spite of very large doses of toxin given during the fall, the downward curve was rapid and persistent.

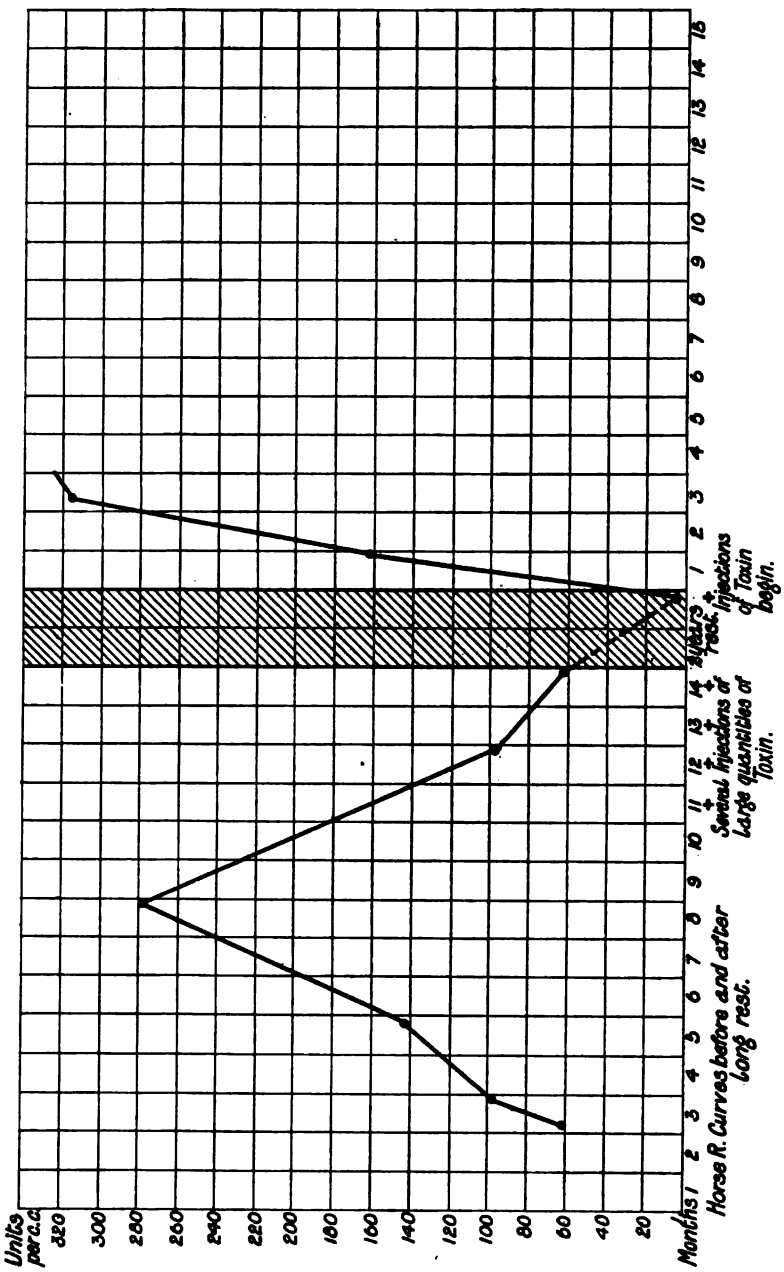

Units per c.c.
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
Months 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Several injections of large quantities of Toxin.
Injections of Toxin begin.
Horse R. Curves before and after long rest.

CHART 5.

An interval of two years, during which the animal received no diphtheria toxin injections, is indicated on Chart 5 by the shaded area.

As is shown in the chart, after one month the animal's serum had reached a strength of 160 units per c.c., and after two months the value was 300 to 400 units per c.c., and appears to be still rising.

It must be mentioned that in both these cases of re-immunisation the toxins were derived from a race of the diphtheria bacillus different from that used in the original immunisation. The toxin used in the primary immunisation was derived from the bacillus used by Behring at Höchst; the toxin in the secondary immunisation was obtained from the bacillus isolated by Park and Williams. The latter gives toxins on an average about five times the strength of those obtained from the former. Whether this could have any influence in the matter it is impossible at present to say.

It is clear then, I think, from these two experiments that animals which have lost the power of producing an antitoxin of useful strength are still capable of recovering that lost power.

This observation has some practical bearings. It seems a fair deduction to make, that when an animal shows a distinct fall in his antitoxin curve the injections ought to be at once stopped, and the animal given a period of rest.

An animal in which the fall has taken place need not be regarded as useless for further diphtheria antitoxin production, as in the department here has hitherto been the case. Theoretically these two experiments are of some importance.

Reverting to Weigert's explanation of the fall in the antitoxin curve, in accordance with Ehrlich's theory, it is clear from the experiments that either the central nucleus of the Seitenketten has not been destroyed as Weigert suggested, or that, if it has been destroyed in certain cells, other cells are capable of taking on the antitoxin-producing function.

November 7th, 1899.

4. *On a new pathogenic streptothrix.*

By GEORGE DEAN.

FROM a review of the recent literature on the subject of Actinomyces and of the Streptotricheæ[1] one is driven to the conclusion that "actinomyces" is a term used to include several different species of micro-organisms. Hitherto there has been a tendency to accept the histological demonstration in the tissues or discharges of club-shaped organisms with a rosette arrangement as sufficient proof that the pathological condition under consideration was due to the presence of one definite organism, the "actinomyces;" but recent researches have demonstrated that any such inference is unsafe.

It has been shown by several observers that widely different organisms in certain stages of their development exhibit filamentous forms with club-shaped swellings on their ends arranged in rosette fashion.

Thus Professor Max Gruber[2] has described an organism, the *Micromyces Hofmanni*, discovered as an accidental contamination, which possessed this characteristic. This microbe was found to be pyogenic in experimental animals, and gives rise, in the lesions produced by it, to the formation of beautiful filaments with club-shaped swellings arranged in rosettes. This organism is quite distinct from any form of actinomyces.

That the tubercle bacillus can present a ray-fungus form in the tissues has been shown by several workers.

[1] Since this paper was sent in for publication a number of communications relating to this subject have appeared. Thus, Lubarsch, "Zur Kenntniss der Strahlenpilze," and Schulze, "Über die Strahlenpilzformen des Tuberculoseerregers," 'Zeitschr. f. Hygiene u. Infectionskrankheiten,' Bd. xxxi, Ht. 1, 1899, have shown that a number of organisms, *e. g.* the *Streptothrix Eppingeri*, the Timothy Grass bacillus, etc., when introduced into experimental animals by the methods suggested by Friedrich and Babes, or by direct inoculation into the kidney, give ray-fungus forms. Levy, "Über die Actinomyces Gruppe (Actinomyceten) und die ihr verwandten Bakterien," and Bruns, "Zur Morphologie des Actinomyces," 'Centralblatt f. Bacteriologie,' Bd. xxvi, No. 1. The latter describes a form of Actinomyces with certain peculiar features. It was altogether non-pathogenic to experimental animals.

[2] Gruber, "Über eine neue Eiterung erregende Microbenart: *Micromyces Hofmanni*," 'Transactions of the Seventh International Congress of Hygiene and Demography,' London, 1891, vol. ii, p. 65.

Friedrich,[1] by injecting an emulsion of tubercle bacilli into the left ventricle through the carotid artery, has obtained a peculiar type of miliary tuberculosis. In the nodules there can be demonstrated, by a special method of staining, "die bacillen inmitten eines schönen Kranzes strahlig angeordneten und so gestalteten Keulen oder Kolben wie wir sie als für Actinomyces characteristisch anzusehen pflegen."

Babes and Levaditi[2] have obtained similar results by injecting an emulsion of an attenuated culture of tubercle bacilli into the meninges and brain of rabbits. A month after inoculation the bacilli are found in masses of filaments having the size and appearance of the granules of actinomycosis. The preparations may be stained in various ways, but good results are obtained by Gram's method and orcein, the filaments retaining the methyl violet, and the rosette of club-shaped processes taking on the orcein stain. Their illustrations represent, as they call it, a veritable "tuberculose actinomycotique."

To pass from forms which are obviously only remotely related to actinomyces, it is clear from the description that the organisms obtained from actinomycosis by some of the chief workers at this subject are distinct varieties if not separate species. Thus Wolff and Israel's[3] streptothrix differs in a number of characteristics from that of Boström.[4] Among other differentiating features of the streptothrix Israeli may be mentioned its superior anaërobic growth, the persistence of bacillary forms in agar cultivations in place of the dichotomously dividing filaments of Boström's organism, and the positive inoculation experiments on animals.

Sauvageau and Radais[5] hold that it is not necessary to assume, as suggested by Boström, that Wolff and Israel were using im-

[1] Friedrich, "Über Strahlenpilzähnliche Wuchsformen des Tuberkelbacillus im Thierkörper," 'Deutsche med. Wochenschrift,' xxiii, 1897, S. 653.

[2] Babes et Levaditi, "Sur la forme actinomycosique du bacille de la tuberculose," Arch. de Méd. expér.,' ix, 1897, 1041.

[3] Wolff und J. Israel, "Ueber Erzeugung mittelst Culturen des Strahlenpilzes," 'Berliner klin. Wochenschr.,' No. xiii, S. 309, 1890; "Über Reincultur des Actinomyces und seine Übertragbarkeit auf Thiere," 'Virchow's Archiv,' cxxv, Heft 1, S. 11, 1891.

[4] Boström, "Untersuchungen über die Actinomykose des Menschen," 'Ziegler's Beiträge,' ix, Heft 1, 1890.

[5] Sauvageau et Radais, "Sur les genres Cladothrix, Streptothrix, Actinomyces, et description de deux *Streptoth. nouveaux*," 'Annales de l'Institut Pasteur,' vi, p. 242.

pure cultures. They state, however, that they consider comparative experiments with the two organisms are necessary.

Kruse,[1] who accepts Wolff and Israel's streptothrix as a cause of actinomycosis, holds that independent confirmation of their results is desirable.

Jurinka[2] states that the cultures obtained by him were identical with those of Wolff and Israel, but the fact that his inoculation experiments were always negative does not tend to confirm this idea.

Kischensky's[3] streptothrix in many points appears to resemble Wolff and Israel's, but inoculation experiments are not described. Kischensky also succeeded in growing his organism on gelatine, which Wolff and Israel failed to do.

Van Niessen,[4] in a recent paper in 'Virchow's Archiv,' still doubts the purity of Wolff and Israel's cultures, and refuses to accept the conversion, in experimental animals, of the bacillary form into filaments with club-shaped processes. He appears to the writer to take altogether too narrow a view of the subject.

Gasperini[5] holds that actinomycosis in the ox is due to different varieties of actinomyces, approaching each other at certain points of their cycle of development, but perfectly distinct at others. He states that certain of these which do not permit of cultivation on artificial media do so after passage through the dog. This is of some interest in relation to the organism described in the present paper, which may have been modified in its passage through the horse.

Eppinger[6] is of opinion that there are probably many species of actinomyces, and regrets that sufficient attention has not been

[1] Kruse, 'Die Mikroorganismen,' Flügge iii, Auflage 1896, Zweiter Theil, S. 57.

[2] Jurinka, "Zur Konservativen Behandlung der menschlichen Aktinomykose," 'Mittheilungen aus den Grenzgebieten der Medizin und Chirurgie,' Bd. i, Heft 2 S. 139, 1896.

[3] Kischensky, "Über Aktinomycesreinculturen," 'Archiv für experimentelle Pathologie und Pharmakologie,' xxvi, S. 79, 1889.

[4] V. Niessen, "Die Aktinomyces-Reinkultur," 'Virchow's Archiv,' Bd. cl, S. 482, 1898.

[5] Gasperini, "Versuche über das Genus Actinomyces, XI Internat. Med. Kong. Rom.," 'Ref. Centralblatt für Bakteriologie und Parasitenkunde,' Bd. xv, S. 684.

[6] Eppinger, "Die Durch Cladotricheen (Streptotricheen, etc.) hervorgerufenen Erkrankungen," 'Ergebnisse der allg. Pathol., Lubarsch u. Ostertag,' Jahrg. iii, S. 328, 1897.

given to the morphological and biological characters of the group. This view is also supported by Unna,[1] who suggests that the clinical types may vary according to the variety of organism present.

It would be undesirable and, indeed, impossible to enter here into a complete review of the literature on the subject of the pathogenic streptotricheæ. A short account, however, of the recent work on the subject is necessary in relation to the present communication.

Of those streptotricheæ which in the animal body produce granules, consisting of filaments with club-shaped endings arranged in rosette fashion, the organisms described by various writers can be seen to belong in the main to two groups, the first closely resembling or identical with Boström's organism, the second, evidently a smaller group, corresponding with Wolff and Israel's. Other organisms with the characteristics mentioned have, however, strongly marked features of their own, and must be regarded as distinct species, *e. g.* the *Streptothrix maduræ* of Vincent.[2]

In addition to these there is a great group of streptotricheæ which do not possess in the animal body club-shaped swellings on the ends of the filaments. This group contains the well-known organisms described by Rosenbach,[3] Eppinger,[4] Schmorl,[5] Nocard,[6] Rabe,[7] and others of less pathological significance.

To this literature there have been several recent additions, indicating a hitherto unsuspected importance of the group as disease-producers.

Garten[8] has described a streptothrix which he isolated from the body of a young man, who for two years had suffered from

[1] Unna, "Aktinomykose und Madurafuss," 'Deutsche med. Zeitung,' No. 6, 1897

[2] Vincent, "Étude sur le Parasite du 'Pied de Madura,'" 'Annales de l'Institut Pasteur,' 1894, p. 129.

[3] Rosenbach, "Über das Erysipeloid," 'Arch. f. klin. Chirurgie,' xxxvi, 346.

[4] Eppinger, "Über eine neue Pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberculose (Cladotrichica)," 'Ziegler's Beiträge,' ix, 287.

[5] Schmorl, "Über ein pathogenes Fadenbacterium (*Streptothrix cuniculi*)," Deut. Zeitsch. f. Thiermed.,' xvii, S. 375, 1891.

[6] Nocard, "Note sur la maladie des bœufs de la Guadeloupe, connue sous le nom de Farcin," 'Ann. de l'Institut Pasteur,' 1888.

[7] Rabe, "Über einen neuentdeckten pathogenen Mikroorganismus beim Hunde," 'Berliner thierärztl. Wochenschr.,' 1888.

[8] Garten, "Über einen beim Menschen chronische Entzündung erregenden, pleomorphes Mikrobion," 'Deutsche Zeitschr. f. Chirurgie,' Bd. xli, Hft. 4 u. 5, S. 257.

necrosis of the vertebræ and ribs with abscesses, empyema, and resulting sinus formation. In the pus were found filaments, long and short rods and cocci. There was no appearance of swellings on the ends of the filaments, of clubs, or of rosettes.

He obtained cultivations on all the ordinary media. From the cultures he got branching filaments dividing into coccal forms without an intermediate bacillary stage. He describes the cocci as having the power of slow movement. In only three animals —two rabbits and one guinea-pig—out of thirty-seven inoculation experiments were positive results obtained.

Sabrazès and Rivière[1] describe two cases in which streptotricheæ were found. The first was the case of a young man who had abscesses in the brain, right lung, and right kidney. Rivière observed filaments arranged in radiating fashion and with rectangular branches in the brain and kidney abscesses, but failed to find those in the lung abscess.

Cultivation on gelatine, potato, and bouillon gave only cocci under aërobic conditions, but anaërobically there developed white, cloudy colonies of the streptothrix. The organism stained by Gram's method. A guinea-pig died of coccus infection, but no other animal experiments are mentioned. The second streptothrix of these authors was obtained from the sputum and from a subcutaneous abscess in pure culture. It was aërobic, grew on and liquefied gelatine, and produced a yellow pigment. It was not pathogenic to experimental animals unless injected along with lactic acid.

Ferré and Faquet[2] isolated in pure culture a streptothrix from a cerebral abscess in an epileptic. It grew well on different media. Both in the pus and from potato cultures it had the form of filaments with knobbed ends staining by Gram's method. It was not pathogenic for guinea-pigs, but, inoculated under the dura mater of rabbits, could be found throughout the whole body without having produced any observable reactive change.

[1] Sabrazès and Rivière, "Sur un Streptothrix rencontré dans un cas d'abscès du cerveau et à un infarctus suppuré du rein," 'La Presse Médicale,' 1894, Sept. 22nd; also "Les parasites du genre Streptothrix dans la pathologie humaine," 'Mercredi Médical,' 1895, pp. 485 and 486.

[2] Ferré and Faquet, "Streptothrix et abscès du cerveau," 'Mercredi Médical,' 1895, p. 441.

Bucholz[1] has described a case of lung disease running a fairly acute course, which he attributes to a streptothrix infection. The clinical picture was one of tuberculous pneumonia and empyema.

The lungs presented the appearance of an advanced tuberculosis chiefly affecting the lower lobes. There were present patches of consolidated tissue which appeared to be necrotic. These had evidently originated from areas of lobular infiltration, and had indurated and atelectic areas surrounding them. There were also cavities containing fœtid pus and communicating with an empyema. These resembled tubercular vomicæ, but had more ragged walls.

The microscopic sections of the consolidated areas gave the appearance rather of a fibrinous than of a tuberculous pneumonia.

Examination of the necrotic areas of the parts round the cavities by Gram's method showed a thick network of delicate branching threads of the thickness of tubercle bacilli. The filaments showed, sometimes complete, sometimes interrupted staining, and here and there a thickening, but there were no coccal or bacillary forms.

In the atelectic regions masses of streptococci were present, but not in the infiltrated and necrotic parts. Neither before death nor at the sectio could tubercle bacilli be found.

Bucholz believes that the streptothrix was the cause of the lobular pneumonia with the resulting necrosis, and that the streptococcus invasion was secondary.

Cultivations failed, owing to the overgrowth of the plates by a variety of proteus. The author explains that the find in the lung was the first indication of the great interest of the case.

Scheele and Petruschky,[2] in a difficult case with multiple skin abscesses, pleuro-pneumonia, cystitis, and pyelitis, in which the diagnosis was thought to lie between glanders and influenza with septicæmia, found in the sputum streptothrix forms. The organism was present in the abscesses in pure culture and grew on gelatine and glycerine-agar, but not, like allied species, on

[1] Bucholz, "Über menschenpathogene Streptothrix, ein Beitrag zur Aetiologie des acuten Lungenzerfalls," 'Zeitschrift für Hygiene und Infectionskrankheiten,' xxiv, S. 470, 1897.

[2] Scheele and Petruschky, "Verhand. des XV Congress für Innere Medicin," ref. 'Deutsche med. Wochenschr.,' Vereins-Beilage, No. 17, S. 124, 1897.

potato or glucose-agar. This is the first time in which a streptothrix infection has been diagnosed during life.

Petruschky[1] briefly referred to a second case, in which a similar organism was isolated from the sputum. It differed from the previous one in giving a more abundant growth on, and in causing liquefaction of, gelatine.

These cases were brought forward at the fifteenth and sixteenth meetings of the International Medical Congress, and the full reports and descriptions have not yet appeared.

Rullmann[2] has described a case from v. Ziemssen's clinic in which, associated with a localised lesion near the root of the right lung, probably of a bronchial gland, there was present in the sputum a streptothrix. It occurred as tough masses composed of interlacing filaments in pure culture. A few of the filaments showed branching. They stained well, though irregularly, with the ordinary bacterial stains, and retained the colour with Gram's method. The organism grew well on all the ordinary culture media.

On Loeffler's blood-serum it produced bullet-shaped colonies which had a chrome yellow-colour. Bouillon culture had a good surface growth, and became turbid. On solidified egg-albumin, aërobically it produced filaments, anaërobically rods with club-shaped ends like diphtheria bacilli.

Inoculation in animals, mice, guinea-pigs, rabbits, gave positive results whether the organism was introduced into the subcutaneous tissues, the peritoneal cavity, the trachea, or the circulation.

In the lesions the filaments were present and could be recultivated. Suppuration of the lymphatic glands was a striking feature of the infection. A horse which was inoculated appeared to be ill for some time, and had a cough, but recovered. Four and a half months after it was killed, and showed in the lungs and liver a few hard nodules, but in these no streptothrix could be found.

This organism is chiefly characterised by the formation of a chrome-yellow pigment on blood-serum, and by the fact that

[1] Petruschky, 'Deutsche med. Wochenschr.,' Vereins-Beilage, xvi, No. 13, S. 78, 1898.

[2] Rullmann, "Über eine aus sputum isolirte pathogene Streptothrix," 'Münchener med. Wochenschr.,' No. 29, S. 919, 1898.

only filamentous forms were present in the experimental animals.

Flexner[1] has described a streptothrix infection of the lung closely resembling that in Bucholz's case in the clinical history, in the morbid anatomy, and in the microscopical character of the organism found in the affected tissues.

The clinical signs and symptoms pointed to a case of pulmonary tuberculosis.

At the *post-mortem* the lungs were found to be partially consolidated, whole lobes being affected. In these areas there was beginning softening (disintegration with early cavity formation). The rest of the lung tissue was congested and œdematous, and contained, scattered through it, caseous areas and calcified nodules. Nodules resembling tubercles and usually translucent were scattered over the peritoneal surfaces, the omentum being especially affected. The mesenteric glands were not enlarged, but on section opaque tubercles were visible in them. Histological examination of the lung showed a cellular exudate, intra- and inter-alveolar, the cells being mostly polynuclear leucocytes. The process of disintegration was extensive, and was characterised by the presence of an increased number of nuclear fragments and irregularly staining detritus. In certain regions the exudate was largely fibrinous. Circumscribed nodules having the size, form, and appearance of miliary tubercles were present in small numbers. They were chiefly composed of epithelioid cells, no giant-cells being found. These were present, however, in the peritoneal nodules, which in their structure closely resembled tubercles. The bacteriological examination revealed the presence of an organism scattered through the affected areas in the form of branching filaments, often in convoluted masses, readily staining by Weigert's method. The branches were sometimes capped at the extremity by a conical swelling. The filaments sometimes stained irregularly, giving a beaded appearance, and rarely showed a tendency to break into short rods.

In the peritoneal nodules the organism took more the form of rods, with a marked tendency to beading. The microbe was

[1] Flexner, "Pseudo-Tuberculosis Hominis Streptotrichia," 'The Journal of Experimental Medicine,' vol. iii, Nos. 4 and 5, 1898.

about the thickness of *B. proteus*. No tubercle bacilli could be found in any of the lesions.

Attempts at cultivation of the streptothrix failed. A guinea-pig injected with a suspension from the consolidated lungs showed no local reaction or enlargement of glands, but wasted and died after nine weeks. *Post mortem* no lesion was found. This experiment is strongly against the view that the process was a genuine tuberculosis, in spite of its great resemblance to that condition.

Notwithstanding the fact that the term "pseudo" has been so widely condemned, it appears inevitable that it should constantly recur in connection with pathological conditions. It has been used in two ways in connection with streptothrix infection, certain cases having been described as pseudo-tuberculosis, as in Flexner's case, others having had the term pseudo-actinomycosis applied to them, as in some of the cases to which reference is about to be made. Sawtschenko,[1] in a case which had the clinical features of actinomycosis, found in the pus granules resembling actinomycotic granules, but which on examination proved to be zooglœa masses of bacilli.

The organism did not stain by Gram's method. It was an obligatory anaërobe, growing on liquid blood-serum, glycerin-bouillon and glycerine-agar at body temperature. It coagulated blood-serum without forming an acid. On admission of O it formed long filaments without branches.

A similar organism, also not staining by Gram's method and not forming branches on cultivation, has been described by Dor[2] from an actinomycosis of the lower jaw. This organism grew on liquid media only, and was aërobic.

Berestnew[3] has also described a case of this nature.

The patient was a child who had the symptoms of broncho-pneumonia. Later there developed an intra-thoracic abscess, which was found, on resection of the ribs, to communicate with

[1] Sawtschenko, "Über Bacilläre Pseudo-Actinomykose" (Russisch), 'Russisches Archiv f. Pathologie,' Bd. i, S. 184, 1896; ref. 'Baumgarten's Jahresbericht,' 1896, S. 613.

[2] Dor, "Une nouvelle mycose à grains jaunes; ses rapports avec l'actinomycose: est-ce une variété de l'actinomycose ou une espèce différente?" 'Gazette Hebdom. de Méd. et Chir.,' No. 47, 1896.

[3] Berestnew, "Über Pseudoaktinomycose," 'Zeitschr. f. Hygiene und Infectionskrankheiten,' Bd. xxix, Ht. 1, S. 94, 1898.

a cavity in the lung. The child died with symptoms of pyæmia. Along with other lesions there were found patches of broncho-pneumonia, cavities in the lung, and a cerebral abscess. In the pus of the brain abscess, and in the broncho-pneumonic foci at the apices of both lungs, was found only one organism, which occurred in granular masses. It took the form of long straight slender rods, not staining by Gram's method. The bacillus proved to be anaërobic, and grew on sugar-agar, and in bouillon mixed with hydrocele fluid.

In liquid media, in addition to rods similar to those found in the pus, it grew in the form of long filaments. It was not pathogenic to rabbits, guinea-pigs, or dogs. It produced in the peritoneum of mice at the site of inoculation foci of suppuration with cachexia and death in about two weeks. In the sections of the affected tissues of the child masses of the organism with radiating filaments at the periphery were found.

These cases, described by Sawtschenko, Dor, and Berestnew, contribute a most interesting addition to our knowledge of pathogenic agents. If their existence is confirmed, they form a group worthy of much wider study.

The other three organisms described by Berestnew[1] were all from cases which would be regarded clinically as typical actinomycosis.

The first was a submaxillary abscess, the second an empyema, and the third a lung actinomycosis. Filaments, clubs, and rosettes could be demonstrated in the discharge from all these.

Berestnew succeeded in cultivating from these cases two microbes which differed essentially from actinomyces, and had also characters which differentiate them from any hitherto described form of streptothrix. The organisms obtained from the first two cases were identical except that the first preferred anaërobic conditions.

It grew on agar and solidified blood-serum in the form of opaque white angular vegetations, which sent processes into the depth of the medium. In bouillon it grew as opaque nodules at the bottom of the test tube, the growth after a week reaching the size of a hemp seed. In this medium it produced an unpleasant odour. No growth could be obtained on potato or gelatine. It died out after two generations.

[1] **Berestnew, loc. cit.**

The organisms from the cultures were found to be mostly rods of very various sizes and shapes, which were often club-shaped, and showed beading. Filaments were also present, which were for the most part unbranched. It was non-pathogenic to mice, rabbits, and guinea-pigs.

The other organism from this group was characterised by producing an intense yellow pigment on agar and by a slow growth on gelatine without liquefaction of the medium. The growth on bouillon in this case occurred in the form of minute particles adhering to the side of the test tube. It also took a bacillary form on artificial media.

In rabbits and guinea-pigs it produced slow-growing infiltrations when injected subcutaneously. On intra-peritoneal injection no effect was produced.

The former of these two microbes described by Berestnew resembles in several features the streptothrix about to be described. There are, however, several points of difference, which will be discussed in a separate section.

Source and isolation of the organism.

The streptothrix was obtained from a horse which was undergoing diphtheria immunisation. Before admission to the stables at The Poplars it was seen by Mr. Villar, F.R.C.V.S., who applied the mallein test with a negative result.

Some time after the animal was discovered accidentally to have a hard nodule below and near the angle of the jaw. The swelling was about the size of a walnut, and appeared to be an enlarged indurated submaxillary gland. The animal seemed to be in excellent health, but, as a precautionary measure, it was again tested with mallein and also with tuberculin, in both cases no reaction being obtained.

The nodule remained apparently unaltered for about three months, and was then observed to be increasing in size. In a week or two from this time it reached the size of a goose's egg, and distinct fluctuation could be made out.

The skin over the swelling was shaved and disinfected, and a sterile hypodermic needle introduced. The pus obtained in this way was mixed with neutral beef tea, and from it a dozen agar, agar-glycerine, and blood-serum tube cultures were made. I

then freely opened and scraped the abscess cavity with a Volkmann's spoon.

The pus which escaped was pale yellow in colour, and the material evacuated resembled the contents of a caseating tuberculous gland. In the pus no granules could be observed.

A number of cover-glass preparations were made and examined for tubercle bacilli, but none could be found.

In preparations stained by Kühne's methylene blue or Gram's method there were observed, fairly uniformly distributed throughout the preparations, delicate filaments which suggested actinomyces. No granules consisting of interlacing filaments, nor clubs, nor rosettes could be found.

The filaments stained irregularly, giving a beaded appearance. They showed true dichotomous branching.

In addition to the microscopic examination, and the preparation of cultures, some of the pus was at once inserted into subcutaneous pockets in the thighs of two guinea-pigs, with the view of ascertaining whether tubercle bacilli were present or not. The result was negative in regard to tubercle. The details will be found in the section on the animal experiments.

The cultivation of the organism.

On the twelve tubes three organisms grew, two bacilli of no interest in regard to the case, and the streptothrix, of which only two isolated colonies could be found, one on the surface, the other in the depth of an agar tube.

From these two colonies sub-cultures were made on various media.

The organism does not grow with great freedom on solid media. Sometimes only one out of six, and often only one out of three tubes of the same media, inoculated from the same culture, develop colonies. The organism tends to die out if it is kept on solid media for several generations, and I have found it advisable to grow it alternately on solid and in liquid media containing blood-serum or ascitic fluid.

This difficulty of cultivating and keeping alive certain species of the streptotricheæ on artificial media has been observed by several writers.

Thus Berestnew,[1] and Mosselman and Liénaux [2] describe species which can be cultivated only in bouillon. Mosselmann and Liénaux's organism could not be kept alive beyond one month.

Agar (surface culture).—The colonies appear from the third to the fifth day as opaque white points. Generally from the outset these have irregular outlines, with angular projections both along the surface of the medium and into its depth. The processes tend to form secondary branches, and in this way a fully grown colony a fortnight to three weeks old presents an appearance like a little mass of white coral, which is very characteristic.

When the surface of the medium is broken in making the inoculation, the growth into its depth is sometimes much more extensive than the surface growth, and presents the same coralline appearance. Sometimes the colony departs from this type, and has a fairly uniform unbroken margin. The maximum size is about $\frac{3}{16}$ inch in diameter.

The colour is an opaque white, with a somewhat wax-like lustre. No change of colour ever takes place in the growth.

Agar (*puncture culture*).—The organism grows well till a depth of about $\frac{3}{4}$ in. from the surface is reached; below this the colonies become very small.

Agar glycerine.—Cultures identical with agar culture.

Agar alkaline (5 c.c. normal NaHO per litre after neutralisation).—Growth somewhat more free than on the above-mentioned media. The appearances are identical.

Glucose agar.—No growth could be obtained.

Bouillon neutral and alkaline (v. alkaline agar).—In these two the results are similar. The growth takes place only at the bottom of the tube, never on the surface or through the medium. The broth appears unaltered. In this case the growth takes the form of a little mass, which after a month has reached the size of a pea, with numerous subdividing processes, so that it looks exactly like a miniature cauliflower or a piece of white coral. Even if, when inoculating the tube, several small pieces of material are introduced, these tend to adhere to one another.

The mass has considerable cohesion and can be shaken about

[1] Berestnew, loc. cit.

[2] Mosselman and Liénaux, "L'actinomycose et son agent infectieux," 'Ann. de Méd. Vétér.' (Brux.), Août, 1889, p. 409.

without breaking. No change in the reaction of the medium can be ascertained.

Yeast medium, as suggested by Spronck,[1] for the diphtheria bacillus, proves an excellent pabulum for the growth of the streptothrix. In this there is less tendency than in bouillon to form one coherent mass. The growth takes the form of a mass of irregularly-branched flocculent particles at the bottom of the tube.

Bouillon with ½ per cent. formate of soda gave a good growth, similar to the last.

Maltose bouillon also proved a favourable medium. Various mixtures of ascitic fluid and normal horse serum (Marmorek's media) with bouillon were tried, and proved themselves very favourable to the growth of the organism.

Sometimes in these it developed like a little semi-transparent mass of textile material with opaque points on it.

Infusions of straw, oats, and hay, with (1) their natural reaction; (2) neutralised; (3) alkalinised, all gave rather poor results.

Milk.—No growth or change in the milk.

Solidified blood-serum.—No growth occurred on the medium, and, as this seemed a remarkable result, it was repeated a number of times and controlled by growing diphtheria bacillus, actinomyces, the first generation of the tubercle bacillus, etc., on the same medium, but always with the same result.

Egg albumen gave no growth either when the egg was inoculated by boring the shell or when the albumen was drawn into sterile Pasteur pipettes.

Potato (1) with its natural acid reaction; (2) alkalinised; (3) glycerinated.—All gave no growth.

Gelatine gave no growth.

The most suitable temperature for the organism was from 35 to 37° C.

The organism grew best under aërobic conditions; anaërobically by Buchner's method with pyrogallic acid the growth was very poor.

[1] Spronck, "Préparation de la toxine diphthérique; suppression de l'emploi de la viande," 'Annales de l'Institut Pasteur,' p. 701, 1898.

The microscopical appearance of the organism from different cultures.

From agar cultures.—Preparations from such cultures were made at intervals from the fourth day till six weeks after inoculation. The appearances did not vary greatly during that time. The organism is seen to be extremely pleomorphic. The great majority of the microbes are in the form of rods, which vary from short, plump rods to long rods about the size of the large form of the diphtheria bacillus. The average may be taken as about 3 to 5 μ in length, ·3 to ·4 μ in breadth.

The rods are often bent, and even spirillum forms may be seen. Club-shaped, battledore, and drumstick forms are present, though not in great numbers.

Many of the rods stain irregularly by Gram's method and by Kühne's or Loeffler's methylene blue and by dilute carbol fuchsin, thus presenting a beaded appearance. The chromatin particles vary from two to five in number.

The forms of the bacilli and the polar staining make the preparations closely resemble those of the diphtheria bacillus; in fact, in many fields of the microscope it could not be distinguished from preparations of the large type of that organism. The bacilli stained by Gram's method or with dilute Ziehl-Neelsen's solution looked larger than when stained by methylene blue. A very few short filaments, which are thicker than the rods, are present, but the picture presented is totally different from what one sees in the case of the ordinary laboratory actinomyces (Boström's), where in a six-days' old preparation the whole field is occupied by a branching network of filaments.

In addition to the form mentioned, a few round, oval, or ellipsoidal bodies are to be found. These bodies have a diameter of about ·8 to 1 μ. Some of them appear to me to be developed on the ends of straight rod forms, others in the middle of the rod. These bodies are of frequent occurrence in this group of organisms, and have been regarded by some as a coccus form, by others as a type of spore.

From bouillon, formate bouillon, straw and yeast media.—The

preparations are practically the same as from agar. The rod form is still predominant, though a few short filaments may be found.

From ascitic fluid or serum bouillon.—Branching filaments are present in greater numbers in this medium. The filaments resemble those from an agar preparation of ordinary actinomyces, but the branching is much less marked.

The filaments stain very irregularly both by Kühne's methylene blue and by Gram's method. Segments of the filaments, often sharply demarcated, and with rounded ends, retain the methyl violet, whereas the adjoining part may be decolourised. By staining by Gram's method and then by Ziehl-Neelsen's carbol-fuchsin, mixed with equal parts of water, one gets very beautiful double staining.

Unlike the bacilli belonging to the tubercle group, this organism, when stained by carbol-fuchsin, shows no resistance to the action of decolourising agents, such as the mineral acids or alcohol.

Summary of animal experiments.

The most successful inoculation experiments were those on rabbits. Out of seventeen rabbits nine gave some naked-eye lesion due to the presence of the organism.

The guinea-pig proved more resistant; only two out of eight gave lesions, and one of these was due to a mixed infection. Of the mice, two animals out of four died, but showed no naked-eye lesion. In one pigeon, out of two inoculated, nodules were produced.

The organism could be obtained in pure form from the lesions twelve and twenty-eight days after inoculation. It was not attempted in every case to recultivate the organism, as this entailed a great amount of labour, a large number of tubes requiring to be made for each case, but in every case a single cultivation was made to exclude the presence of other organisms, such as the pyogenic cocci. This result was confirmed in every case by the microscopical examination of the lesions.

The method that gave the largest number of positive results was intra-peritoneal injection; eight out of eleven rabbits were

so infected. In a number of these a subcutaneous lesion also was produced at the site of inoculation.

Intra-venous injection either failed to give any result or the animal died without any observable lesion, perhaps from some toxic effect. This happened in three out of six experiments.

Affanassiew and Schultz,[1] with a streptothrix isolated by them, got similar results with old cultures, probably from some toxic substance contained in them.

The most important facts pointing to a toxic action were obtained by me in the case of three rabbits which were inoculated from a flask in which the streptothrix had been grown for twenty days in bouillon containing ½ per cent. formate of soda. These animals died with cachectic symptoms in twenty, twenty-two, and twenty-four days after inoculation, and no lesion to account for death could be found. (Formate broth alone does not produce any such effect.) This may be a coincidence, but it was remarkable that the three animals should die in so nearly the same time and without any other apparent cause to explain the circumstance.

In other cases filtered bouillon cultures produced in the ears of rabbits a marked local inflammatory reaction with formation of vesicles.

Naked-eye appearance of the lesions.[2]

The lesions took for the most part the form of tubercular-looking nodules varying from the size of a millet seed to that of a horse-bean. In the omentum they were arranged like a bunch of grapes. They were pale yellow in colour, in some cases with a surrounding halo of injected vessels. Certain of the larger nodules contained a thick caseous purulent-looking material.

In the case of one rabbit the lesion was in the form of an elevated plaque on the peritoneal surface of the cæcum. The organism when injected directly into the renal substance gave rise to necrotic areas.

[1] Affanassiew and Schultz, "III Med. Cong. Russ.," ref. 'Baumgarten's Jahresbericht,' Bd. v, S. 398.

[2] For protocols of animal experiments *vide* 'Transactions of the Jenner Institute,' vol. ii, wherein, also, figures of the micro-organism are published.

The sites of the lesions were at the point of inoculation in the subcutaneous tissue, on the parietal, and on the visceral peritoneum on the omentum, and at the hilum of the spleen.

Structure of the lesions in the experimental animals.

The nodules and affected tissues were fixed and hardened either in alcohol or in Zenker's solution, and then embedded in paraffin in the usual manner.

The ordinary histological stains were employed in examining the structure. For demonstrating the organism in the tissues the best results were got by Gram's method (Weigert's modification), alone or combined with picro-carmine or eosine. Very beautiful results were obtained in this manner.

The Erhlich-Biondi stain and Plaut's fuchsin and picric acid method both gave excellent results.

Examination of lesion in early stages, say seven days after inoculation.

The organisms in this case still retain the bacillary form. Branching filaments are present, but are not numerous. The organisms are surrounded by masses of fibrin, hæmorrhages, and groups of polynuclear leucocytes. There is an active proliferation of fibroblasts in the neighbouring connective tissues.

Tissues, such as the kidney, into which the organism has found its way, are in a necrotic condition. The cells in these areas are blurred and stain badly. The necrotic tissue has sometimes a considerable amount of fibrin deposited in it, as shown by Weigert's method. The affected parts are surrounded by a hyperæmic zone. In and near the necrotic tissues the organism is present in considerable numbers.

Examination of lesion at more advanced stage, from twenty to thirty days after inoculation.

At the periphery of the nodule there is a capsule consisting of young fibrous tissues, fibroblasts, and spindle-cells. From this capsule a number of septa, with the same structures, pass into

the nodule and subdivide it. The spaces thus formed contain a mass of cells, for the most part polynuclear leucocytes, with a few so-called "epithelioid" cells. Remains of hæmorrhages and traces of fibrin may still be present. Among these structures the organism is found in various stages of its development. The bacillary and coccal forms are still represented, though in much smaller numbers.

Filamentous forms are now predominant. They are most frequently arranged in dense interlacing clumps, with the ends of a number of the filaments radiating from the periphery. This is the pre-rosette stage, in which the ends of the filaments have not yet assumed the flask or club-shaped swelling. In other groups these have gone on to form well-marked clubs arranged in rosette fashion with a zoogloœa-like mass in the centre. In comparing the clubs with those found in the tongue of the ox, one is struck by the frequency with which in the rabbit this organism gives rise not to a blunt but to a lanceolate club, the point of the spear-shaped process pointing outwards. I do not mean by this to assert that the organism is characterised by this form, but its frequency is certainly remarkable.

The clubs when stained by Gram's method retain the methyl violet well.

Gasperini[1] found in experimenting with actinomyces on a calf that the clubs developed in four days, but in one of my rabbits, which died on the seventh day, I could find only bacillary, coccal, and a few filamentous forms.

It was interesting to find that in the pigeon, even after twenty-four days, there was no formation of clubs or rosettes, the organism having remained in the stage of convoluted branching filaments.

Examination of lesions two months old.

In nodules of this age there is a tendency to cavity formation in the centre of the nodule. This is surrounded and partly filled by badly staining granular *débris*. Outside this the "epithelioid" cells are now more numerous.

A few giant-cells packed with fragments of filaments can in some sections be found near the margin of the cavity.

[1] Gasperini, "Nuove ricerche sull' actinomicosi sperimentale," 'Annali d' Igiene speriment.,' vol. vi, p. 475.

The organism is now almost entirely in the club-shaped or spear-shaped form. A few filaments with globular swellings in their course are present. There are to be seen in the nodule at this stage numerous spherical hyaline bodies, which stain deeply by Gram's method and also with carbol-fuchsin. These vary in size from minute points to about the size of a red blood-corpuscle.

The differential characters of the streptothrix from those nearly allied to it.

The streptothrix resembles the *Micromyces Hoffmanni* in giving no growth on potato, gelatine and blood-serum, and in producing subcutaneous lesions in rabbits containing the rosette form; but differs from it in having the characteristic coral-like growth, especially in bouillon, instead of a powdery deposit, in producing no brown pigment, and in giving rise to distinct lesions when inoculated intra-peritoneally, which the *Micromyces Hoffmanni* fails to do.

The streptothrix resembles the *Streptothrix Israeli* in having persistent bacillary forms on agar and in the positive inoculation experiments on animals, but differs from that organism in its characteristic coralline growth, especially in bouillon, by the absence of growth on egg albumen and blood-serum, and markedly by a distinct preference for aërobic conditions, and by showing under these greater rapidity and freedom of growth.

The last feature alone is sufficient to differentiate the two organisms.

The *Streptothrix alba* of Rossi-Doria (*Actinomyces bovis albus* of Gasperini) [1] is readily distinguished, as it forms a membranous growth on gelatine with liquefaction of the medium.

Berestnew's [2] organism from his first two cases of pseudo-actinomycosis resembles in a number of features the organism we are considering, but its cultural characters, the fact that it died out so quickly and that it was not pathogenic to rabbits, guinea-pigs, and mice, are sufficient to differentiate it.

[1] Gasperini, "Versuche über das Genus Actinomyces," ref. 'Centralblatt für Bakter.,' xv, S. 684.

[2] Loc. cit.

Berestnew's third organism is distinguished by the production of a yellow pigment on agar, and by the occurrence of growth on gelatine. From the short review of the literature given it will be seen that the other forms recently described have features quite distinct from the present organism.

I have compared cultures on various media and microscopical preparations of the streptothrix with those of actinomyces obtained from three different sources.

(1) From Dr. Salter, cultivated from an appendicitis in the human subject.

(2) From the Jenner Institute at Chelsea, of unknown origin.

(3) From Kràl, Prague, from the human subject.

I found these three to be practically identical with one another, and to be widely different from the streptothrix. The growth in all of these is much more abundant and rapid; they all grow on potato and on gelatine with liquefaction of the medium, and on potato and agar they produce pigments, yellow and brown of various shades, and black. The microscopical characters of the growth have been already referred to. The organism has also been compared with all the members of the group which it has been possible to obtain, namely, *Streptothrix Nocardii, Streptothrix Eppingeri, Streptothrix nigra, Streptothrix canina,* but to none of these does it present any marked resemblance.

Conclusions.

(1) That the organism described in this paper produced in the horse a disease which might be descibed clinically as actinomycosis.

(2) That, resembling certain described forms, this streptothrix has characteristics which differentiate it from these.

(3) That it differs widely from the ordinary actinomyces of the laboratory.

(4) That the organism has a bacillary form which persists on agar, etc.

(5) That the bacillary form introduced into experimental animals gives rise to nodules, and in those are developed filaments with lanceolate and club-shaped processes arranged in rosette

fashion, thus confirming Wolff's and Israel's results with an allied organism.

(6) That certain of the experiments recorded in this paper point to the production of toxins by the streptothrix.

(7) That the results obtained in this research tend to confirm the hypotheses (*a*) that the streptotricheæ are more nearly allied to the bacilli, such as the diphtheria and tubercle bacilli, than to the moulds; (*b*) that actinomycosis is a disease due not to one specific micro-organism, but to a number of allied species.

November 7th, 1899.

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5. *The occurrence of the* Bacillus proteus vulgaris *in a venous thrombus.*

By W. C. C. Pakes.

The *Bacillus proteus vulgaris* is not uncommonly associated with other bacteria in abscesses in various parts of the body. It is also very commonly associated with *post-mortem* decomposition, some forms of infantile diarrhœa, cystitis, Weil's disease, and puerperal sapræmia. In spite of the number of cases in literature in which this organism has been found, there are very few in which it has been found in pure culture, and still fewer in which it has been found in the blood.

Foa and Bonome[1] described a case of hæmorrhagic enteritis with peritonitis and venous thrombosis, in which they found a very virulent culture of the *B. proteus vulgaris*. Crogius[2] and Schnitzler[3] found a universal infection with this organism following a proteus cystitis.

The following case was under Dr. Newton Pitt in Guy's Hospital, and I am indebted to him for permission to publish some of the particulars of the case.

Florrie H—, aged 13, was admitted for swollen left lower

[1] "Sur les maladies causées par les Micro-organismes du genre Proteus (Hauser)," Archives Italiennes de Biologie,' t. viii, p. 219.

[2] 'Recherches bactériologiques sur l'infection urinaire,' Helsingfors, 1892.

[3] 'Aetiologie der Cystitis,' Wien und Leipzig, 1892.

extremity and anæmia, and was suffering from phthisis and tuberculous enteritis. Thrombosis of the left iliac vein was diagnosed. A week before she died the right leg began to swell owing to thrombosis of the right iliac vein. The urine was tested several times and was always normal, and there were never any signs of cystitis.

The autopsy was made by Dr. Fawcett, who found an old organised clot in the left femoral vein, and one which was just commencing to organise in the right. Recent thrombosis in the right and left iliac veins and recent infarcts in the kidneys were also present.

A portion of the left iliac vein was ligatured and removed intact. The outside of the vein was carefully sterilised and cut open. Microscopic preparations, cultures on agar broth, glucose broth, and gelatine plates were made.

The microscopic preparations showed a fairly large number of bacilli, which were almost entirely decolourised after treatment by Gram's method.

The cultivations showed only one organism, which gave the following reactions:

Description of the bacillus.

A fairly motile bacillus varying considerably in length.

Stained by van Ermengem's method it showed from four to ten or twelve flagella.

No evidence of spore formation could be observed.

It failed to retain the stain after treatment by either Gram's or Weigert's method.

Cultures:

Broth.—This was rendered universally turbid, and gave an indol reaction after five days.

Gelatine.—A very rapid growth and liquefaction took place, the liquefaction taking place in the depth as well as on the surface of the medium; a few bubbles of gas were seen in the gelatine.

Agar.—A thin, moist, translucent growth was found, which had spread over the whole of the surface in twenty-four hours.

Blood-serum.—On this medium a grey, moist growth took place, which in three days began to liquefy it, giving rise to a putrefactive odour.

Potato.—A grey, moist growth.

Litmus milk.—After twenty-four hours there was a slight acid reaction. At the end of three days a soft clot was formed, which had been dissolved at the end of ten days.

Nitrate broth.—After twenty-four hours' growth fairly abundant nitrites were found.

Urine was rendered turbid, and a very alkaline reaction was produced with the formation of crystals of "triple phosphate."

Peptone solution, glucose, lactose, saccharose broth.—All these showed slight acid and considerable reduction.

Glycerin broth gave slight acid but no reduction.

Iron agar and *broth* showed the presence of considerable sulphuretted hydrogen.

The organism grew well under strictly anaërobic conditions.

The question which now arises is, whether this bacillus was the cause of the thrombosis or was really a *post-mortem* incident. There is no doubt that the organism is very frequently found in the body after death, and after the lapse of some days can be found universally distributed throughout the body. In this case the body showed no signs of marked decomposition, and in such an event the *Proteus vulgaris* is not commonly found in the blood. Further, this organism was found in considerable numbers in the smears from the clot, and if this had been the condition all over the body it is quite certain that marked decomposition must have taken place.

There are several points which indicate, I think, a causal relationship between the bacillus and the thrombosis.

In the first place, this organism is not infrequently found associated with other organisms in abscesses. Secondly, there appears to be no reasonable doubt that it can alone produce cystitis. Thirdly, it is probably a common cause of puerperal sapræmia.

It cannot therefore be looked upon as quite harmless. In the present case the history of the thromboses seems to me to point to some bacterial origin, and I believe that many of the thromboses occurring late in a wasting disease would be found to have a bacterial origin if they were examined.

In health the bactericidal power of the blood is probably sufficiently great to destroy this organism if it should gain access to it, but when from any cause this action is diminished the

organism becomes relatively pathogenic. The bactericidal power may be reduced in many ways, of which a wasting disease and a dose of ptomaines are two.

If Krogius' and Schnitzler's cases are accepted as general infections following cystitis, there is no reason why this cannot be looked upon as a case of slighter infection coming from the lung, which contained numerous cavities, or from the intestine. The *Proteus vulgaris* is frequently to be found in the lungs and fæces in such conditions, and could easily get into the blood.

I have searched through a considerable amount of literature on the subject, and it seems that very little is known of the cause of many of the cases of thrombosis. I would venture to suggest we should add very much to our knowledge if every available thrombus were examined bacteriologically.

January 16th, 1900.

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6. *The bacteriological examination of a thrombosed ovarian vein (following hysterectomy).*

By T. G. Stevens, M.D.

J. S—, aged 47, was operated on by Dr. Galabin for a large fibromyoma of the uterus. Abdominal hysterectomy by Baer's method was performed. The patient survived the operation eleven days, and eventually died of a subacute form of septicæmia. At the *post-mortem* examination the right ovarian vein was found to be thrombosed from the ligature up to its entrance into the vena cava. Cultures were taken from the interior of the vein in the following manner:—The peritoneal cavity having been emptied of its contents—liver, stomach, intestines, etc.—the vein was exposed, and its surface, as well as the peritoneum around, was seared with a hot iron. The vein was then opened with a pair of sterilised scissors, the edges held apart with sterilised forceps, and a broth tube inoculated at once with a sterilised platinum loop from the breaking-down clot in the vein. The broth tube was placed in an incubator at 34° C. for twenty-four hours. After this interval the broth was uniformly clouded

with growth, which, on examination in a hanging drop, showed short bacilli, long bacilli, and streptococci. Gelatine plates were inoculated from the broth tube in the usual way and incubated at 18° C. Plate No. 2, at the end of twenty-four hours, showed three kinds of colonies: (*a*) typical colonies of the *Bacillus coli communis* group; (*b*) streptococcus-like colonies; (*c*) a liquefying fluorescent organism. When transplanted on to agar and broth, (*a*) and (*b*) showed only growths indistinguishable from *Bacillus coli communis;* no streptococcus colonies were found. On agar (*c*) produced a white growth with a brilliant green fluorescent coloration of the medium. In milk, coloured faintly with litmus, it gave proof of intense acid reaction, and completely clotted the medium; on gelatine, white liquefying colonies, with the fluorescent green pigment in the medium; in broth, a yellowish-green turbidity. All these growths microscopically were made up of short bacilli. From these cultures and the microscopic appearances the organism was judged to be the *Bacillus pyocyaneus.* Could this condition have been diagnosed as one of thrombotic pyæmia, I feel sure that, from the *post-mortem* appearances, the vein could have been easily dissected out, and possibly the fatal result might have been averted. I put forward this suggestion tentatively, and with every regard to the desperate condition that this patient was in, in the hope that thrombosed veins in accessible positions may be more frequently examined bacteriologically, as a help to the surgeon in performing operations for the relief of such cases.

January 16th, 1900.

7. *Mycotic "tumour" from a horse.*

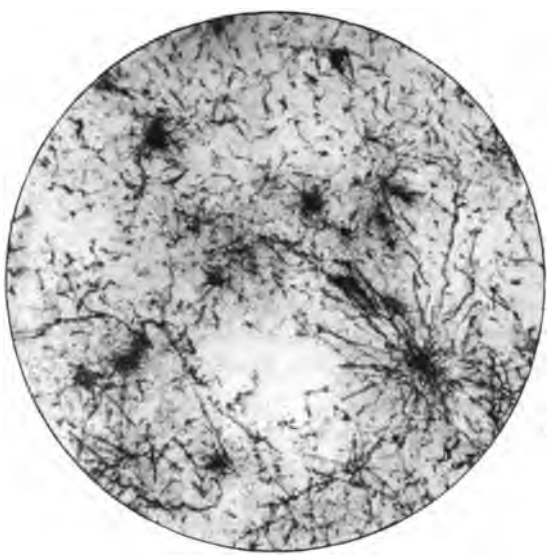
By Alexander G. R. Foulerton.

This specimen, which Mr. Bland-Sutton very kindly handed over to me for examination, is a tumour which occurred in the maxillary sinus of a horse. The tumour is of an irregularly oval shape, measuring 10 centimetres in the longer, and 8·5 centimetres in the shorter diameter. It consists of a centrally placed

core of soft caseous material enclosed within a mass of extremely hard dense tissue. This outer layer, which measures from 2 to 4·5 centimetres in thickness, is formed of closely set fibrous tissue, with here and there a little calcareous matter. The soft central portion consists mainly of small star-shaped masses of mycelium embedded in a rather scanty ground substance, which latter stains badly—or not at all—and shows no evidence of definitely organised structure. No trace of mycelium is to be found in the outer fibrous layer.

The pathogeny of the tumour is probably as follows:—The outer fibrous mass represents the overgrown wall of a suppu-

FIG. 1.



A section through portion of the central caseous mass. The ground-substance is not apparent, the mycelium of the parasite alone being stained. Magnified 120 times. From a photograph by Mr. Barnard.

rating cyst, attached at one time to the fang of a carious tooth. The central core represents the inspissated contents of the cyst cavity, which had become invaded by a mould parasite from the mouth.

The specimen is, perhaps, chiefly of interest as an example of tumour formation resulting from what one must call—for want of a better term—chronic irritation. The micro-organism which is contained in the central core is clearly a mould fungus; but

since there was no opportunity of making cultures I do not feel able to express any opinion as to the exact species. The mycelium stains well with hæmatoxylin and with basic aniline and some, also, of the acid aniline dyes; it does not stain by Gram's method. The mycelial threads radiate outwards from a common centre in each mass; they are of considerable length, and are fairly straight, giving off lateral branches at intervals. Individual lengths of the mycelium differ considerably from each other in thickness, but each one is fairly uniform throughout. There is no appearance of thickening at the extremities of the lateral branches, nor is there any evidence of sporulation.

The general character of the tumour, the thickness of much of the mycelium, and the fact that the latter does not stain by Gram's method, all appear to indicate that the parasite is not the common ray fungus (*Streptothrix actinomycotica*) found in the horse and other animals. Nor could the fungus possibly, I think, be confounded with any of the aspergillar species which are known to infect the horse, and an example of which I showed before this Society last year.[1]

Too much stress should not, perhaps, be laid on the fact that the mycelium does not stain by Gram's method, since it is obvious that the growth of the fungus must have been of considerable age at the time of death. And it is well known that some of the streptotricheæ, including *S. actinomycotica*, which normally stain by Gram's method, lose this staining property in old cultures, in which one finds considerable portions of the mycelium which do not take the stain. Such loss of staining property is, however, so far as I know, always coincident with the occurrence of "chain-sporulation," of which process there is no evidence in this specimen.

Finally, in this case there cannot be any question as to the fact of the parasite having existed within the tumour during the life of the animal, and of not having merely invaded the tissues after death.

January 16th, 1900.

[1] "Mycosis (Aspergillar?) of Lung of Horse," 'Path. Soc. Trans.,' vol. l, 1899.

8. *A supra-patellar sesamoid bone.*

By Edred M. Corner.

[With Plate I.]

The accompanying skiagraph illustrates what may be regarded as a very rare, if not unique, condition in the human subject. At the upper limit of the trochlear surface of the femur and above the patella an additional bone may be seen in the extensor tendon. The skiagraph is of the right knee of a man aged 22, whose occupation was that of an omnibus conductor. The left knee exhibited nothing abnormal. That this osseous nodule has resulted from a transverse fracture of the patella is an obvious suggestion, which is emphasised by the condition being unilateral. The patient, moreover, gives a history of injury to this knee. The injury occurred at his work, and resulted in the joint becoming swollen. But the swelling lasted only for a few days, and he could get about during this time. Since then his knee is liable to become swollen and painful upon any slight twist, and it was this that brought him to the hospital. In no detail does the history bear out the suggestion that such an injury as fracture occurred, but rather some synovitis or displacement of a cartilage. His age, twenty-two, is young for the occurrence of fracture, and again, the situation for a fracture is unusual. The patient discovered the extra bone quite recently, and did not connect it with the injury. The exact date of the injury he could not state, but said that it occurred about a year ago. There was no wasting of the extensor muscles of the thigh on the right side. Considering the history it seems improbable that such a severe injury as a fracture ever occurred.

On examining the skiagraph it will be seen that the extra bone is much thinner than the patella and is consequently most unlikely to represent the broken off upper fragment. Also the corresponding surfaces of the two bones do not present the sharp cut appearance found in transverse fractures. Again, the sum of the two bones would be too large and would present a most un-

DESCRIPTION OF PLATE I,

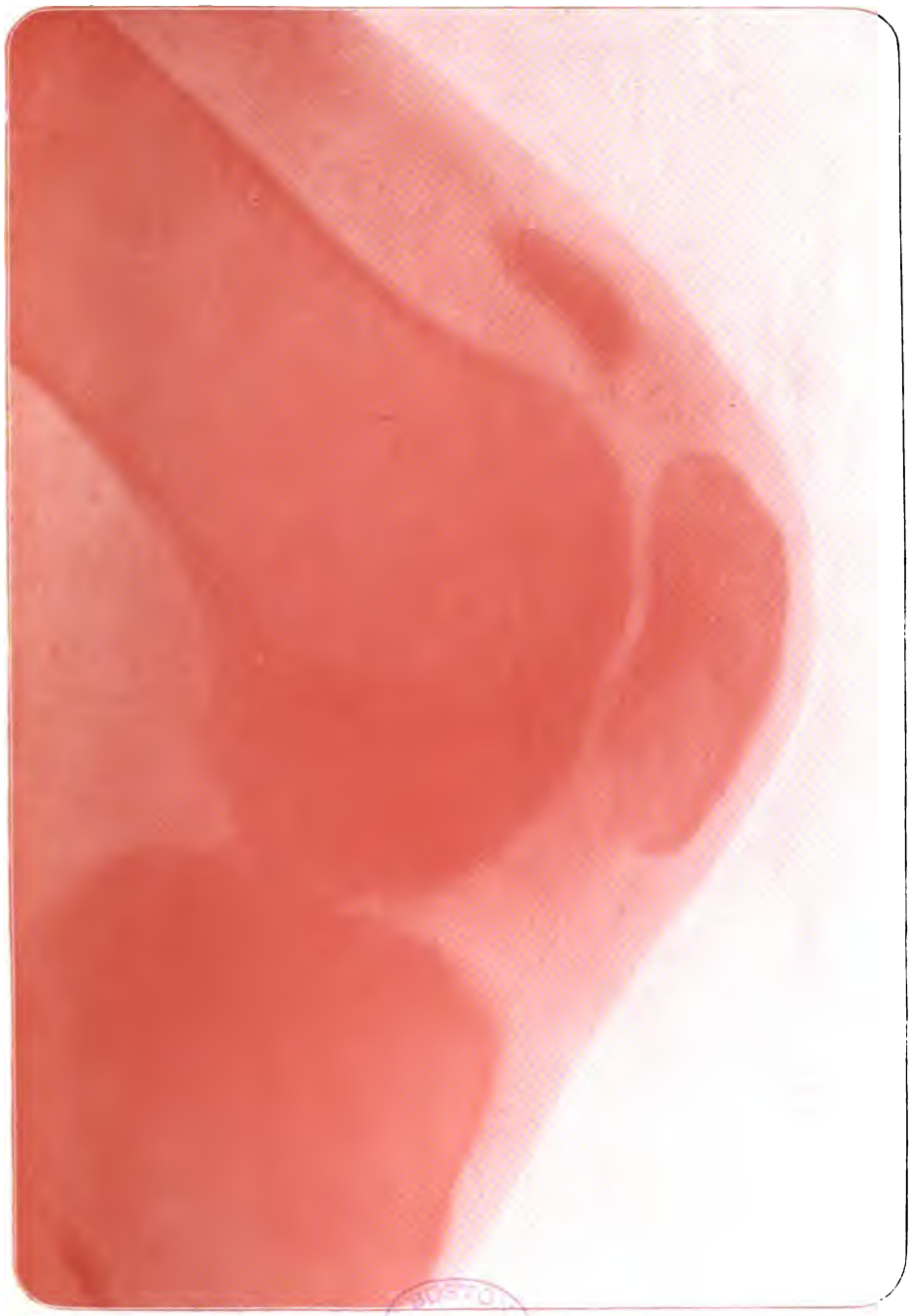
Illustrating Mr. E. M. Corner's case of Supra-patellar Sesamoid Bone. (Page 54.)

The skiagraph shows a supernumerary ossicle lying in the tendon of the quadriceps extensor, and separated by a distinct interval from the patella, which is normal in size and form.

EXPLANATION OF PLATE I.

Fig. 1. Mr. Turner's case of Supra-patellar Sesamoid.

Fig. 2. Supernumerary ossicle lying in the tendon of [illegible] separated by a distinct interval from the [illegible] of size and form



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gainly patella, entirely at variance to that found in the opposite leg.

On examining the records for similar cases, I was unable to find one which corresponded to the one I have related. Grüber in 'Virchow's Archives,' No. 94, p. 358, 1883, described a case of patella bipartita in a young man. In this case the condition was bilateral, and it was the superior external angle that was separated from the rest of the bone. The condition was apparently congenital, and there was no history of injury.

In the anthropoid apes a fibro-cartilaginous body is normally found in the extensor tendon, above the patella (Keith). The extra sesamoid that I have described may represent this, though I have been unable to find any such body in the examination of fœtal knees. Another view may be put forward which almost certainly explains Grüber's case. The patella normally ossifies from one centre, that appears about the third year of life. More than one centre occasionally appears, and it may be that the extra bones represent a centre that has failed to unite with the body of the bone. Although the patella is developed in cartilage, it is now usual to agree with Albrecht ('Inaugural Dissertation,' Kiel, 1875) that it is a sesamoid bone, and is consequently of little or no morphological significance. Sesamoid bones, although of no morphological value, are essentially of mechanical importance. Hence the view that the extra bone described in this paper may be a new formation developed for mechanical reasons is erroneous, as the condition is unilateral.

As the mechanical and morphological views are improbable, the best explanation for the presence of the supra-patellar sesamoid bone seems to be that it represents an additional centre of ossification that has failed to unite with the body of the patella.

The case was exhibited at the Medical Society, November, 1898, by Mr. Battle, to whom I am indebted for the further use of it, and to Dr. Barry Blacker for the skiagraph.

January 16th, 1900.

9. *A specimen of "spontaneous" carcinoma of the uterus in the rabbit, with a criticism of the mechanical hypothesis of the origin of carcinoma.*

By Samuel G. Shattock.

[With Plate II, fig. 1.]

The interest attaching to this specimen relates almost exclusively to the bearing it has upon the experiment put on record by Dr. Lambert Lack in the 'Transactions' of the Jenner Institute, vol. ii, and the 'Journal of Pathology,' August, 1899, p. 154.

And I may, therefore, after describing it in detail, offer some criticism upon Dr. Lack's experiment, and the hypothesis Dr. Lack supports.

The uterus was removed from a rabbit upon which no operation or experiment of any kind had been performed, the animal having been killed owing to its being obviously diseased.[1] There were a certain number of nodules in the peritoneal cavity; the thoracic viscera were not inspected. As viewed externally the long uteri (of which in the rabbit there are two, opening separately into a single vagina) are much enlarged, tortuous, and deformed by the growth of large nodular swellings, one uterus being considerably more diseased than the other. At one spot the more diseased has a maximum diameter of 3 cm.

The enlargement is not uniform or continuous, but occurs in nodes with intervening constrictions. Some of the enlargements overhang their base, but all are smoothly covered with peritoneum. On slitting up each uterus, the masses of new growth, some sessile, others pedunculated, are found to project within and considerably distend the canal. There are scarcely any areas of the uterine mucosa between the actual tumours that are not obviously abnormal, the membrane being papillary and cystic; some of the cysts project far from the surface, which to some extent recalls that of a chorionic mole. In these areas, nevertheless, the muscular wall is readily traceable, intact,

[1] The preparation is now in the Museum of the Royal College of Surgeons.

Fig. 1.

Fig. 2.

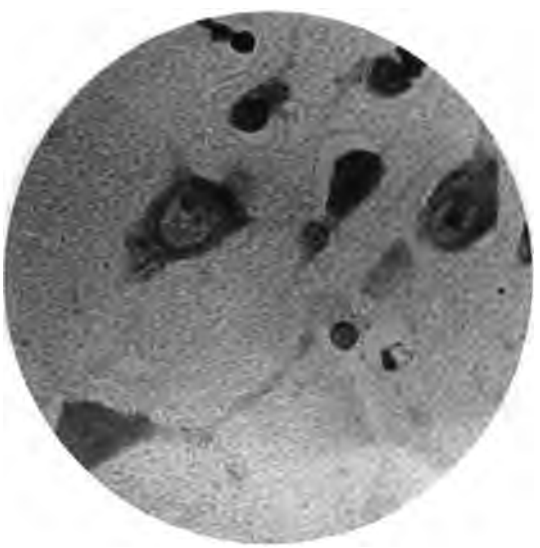

Fig. 3.

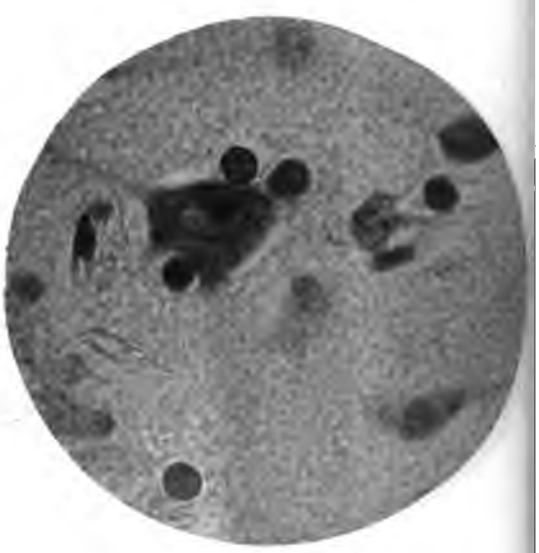

Fig. 4.

DESCRIPTION OF PLATE II.

FIG. 1.—Illustrating Mr. S. G. Shattock's communication on "Spontaneous" Carcinoma of the Uterus in the Rabbit, etc. (Page 56.)

FIGS. 2, 3, 4.—Illustrating Dr. Bertram Abrahams's paper on the Cortical Changes in Acute Chorea. (Page 94.)

FIG. 1.—A section of uterine carcinoma from the rabbit; the growth is in places papilliferous.

FIGS. 2, 3, 4.—Sections from the right parietal lobule in a case of chorea gravidarum.

FIG. 2.—Small pyramidal cells with enlarged perineuronal spaces and some excess of lymphocytes. The cells are slightly swollen and bulged, and their nuclei somewhat pale.

FIG. 3.—Medium-sized pyramidal cells showing similar changes. The deep staining of the nucleolus is well seen, the nuclei being but little coloured.

FIG. 4.—Large pyramidal cell with convex contour, indistinct processes, and faint diffuse granulation. In the dilated perineuronal space are three lymphocytes.

beneath, the morbid condition being strictly limited to the mucosa, and not as yet indisputably malignant.

In the diseased mucosa the carcinomatous growths arise; some such are lowly projecting swellings which still present a villous and cystic surface, but on section appear as solid neoplasms involving the entire thickness of the muscular wall.

In each uterus the disease ceases above the internal os, *i. e.* for the length of a centimetre above the external os the mucosa is lax and longitudinally folded, though here and there a low cystic eminence will present itself ("ovula Nabothi").

The vagina is quite normal.

Pathological histology.—The growth is a columnar-celled carcinoma, in many situations of the villous or papilliferous variety; and in general characters it resembles the papilliferous carcinomata met with in the thyroid, breast, or rectum, and the similarly constructed adenoma of the ovary. The section presents a series of thin-walled spaces of various sizes and form, the walls of which consist in part of connective tissue, but largely, also, of the unstriped muscle-fibre of the uterine wall, the entire substance of which is invaded by the growth. In certain areas the interior of the several spaces is rendered very complex by a highly-developed system of papillary infoldings, the narrow clefts between which are in places filled with extravasated blood.

In the midst of the papilliferous portions there occur younger foci, which consist of closely-set, narrow, simple winding tubules lined with a single layer of cubical epithelium; in a still younger stage the cell columns are devoid of lumen. The epithelium which lines the spaces and invests the processes is for the chief part cubical, but in certain areas it is of a long columnar kind, and whatever its character it is disposed in a single layer.

The morbid condition of the mucosa as studied beyond the carcinomatous formation consists in the papillary upgrowth of connective-tissue processes covered with columnar epithelium, and of various grades of complexity. This condition is followed by tubular ingrowths, furnished with a lumen, towards the muscular coat; in some such, cyst formation has arisen from the retention of secretion. These tubular extensions in the next stage invade the proper muscular tissue.

The whole process proceeds exactly as is witnessed in a columnar-celled carcinoma of the rectum, the likeness being further increased by the manner in which growths of the last-named part are at times papilliferous. The papilliferous character varies in different parts; in some nodules it is absent, the whole area consisting of closely-set tubular spaces lined with columnar or cubical epithelium.

Beyond such "pre-cancerous" areas the mucosa may be normal, and present only a regular series of low elevations provided with short simple glands, the epithelium being throughout columnar. The abnormality of the papillary condition is obvious on comparing the sections with those of the normal uterus of the rabbit, whether in the unimpregnated or pregnant state.

It is not possible in the face of such a wide distribution to determine whether the disease arose in many independent foci, or as a single primary tumour from which an auto-inoculation of the mucosa by means of the shed cells took place. The fact that the cervix of each uterus is unaffected, whilst the disease is far advanced in the body of each, points to an independent source of the lesions on the two sides.

Dr. Lack's experiment, and the mechanical hypothesis of the origin of carcinoma.

Dr. Lack's experiment was carried out as follows:—Under ether, the peritoneal cavity of a rabbit was opened, the ovaries grasped, cut open, and the raw surfaces scraped firmly with the sharp edge of the knife; the milky juice, containing free epithelial cells, thus obtained, was carefully allowed to diffuse through the peritoneal cavity. The rabbit remained well for nearly a year; it then became thin and weak, and commenced to suffer from dyspnœa; two months later it was killed. The abdominal cavity was found studded with carcinomatous nodules, and small white foci were thickly scattered through the liver.

The uterus was greatly thickened; the mucous membrane papilliform, and at one place in the wall was a tumour as large as a cherry. There were other foci in the thorax. The condition of the ovaries is not stated.

The various new growths showed the structure of columnar-celled carcinoma.

This is the experiment; and the hypothesis is that the dis-

placement of *normal* epithelium into a lymph space or lymph cavity is sufficient to bring about the growth of a carcinoma.

The most ominous feature in the *post-mortem* finding is the condition of the uterus; for the state of the mucosa is precisely like that in the specimen exhibited, in which it is easy to trace the source of the carcinoma of the uterine wall from the morbid mucous membrane; the size, again, of the uterine tumour exceeds that of the peritoneal growths; nor is a sufficient histological account of the uterine changes furnished to enable a reader to judge whether the tumour noticed was the only carcinomatous formation present in the uterus, or one of others that may have escaped notice because less prominent.

The author, it is true, speaks of the structure of the various tumours as corresponding with that of "ovarian carcinoma," as though there were something unique and diagnostic in the latter. But this cannot be allowed, for similar columnar-celled papilliferous carcinomata are met with not only in the thyroid, breast, rectum, laryngeal glands[1] (?), kidney, etc., but, what is most to the point, in the uterus of the rabbit itself.

In coming to his conclusion as to the causal relationship between his experiment and the disease found after death, Dr. Lack was influenced largely by the statement of Professor J. McFadyean, that he (Professor McFadyean) had never seen or heard of carcinoma in the rabbit. The present specimen not only shows that carcinoma occurs in the rabbit, but the uterine changes and the structure of the carcinomata are so alike in the two cases that a repetition of Dr. Lack's experiment is rendered absolutely imperative. And unless this striking result can be repeated, it must be passed by as a coincidence, remarkable enough, but not without parallel, as the historical error of Hunter suffices to show.

Hunter, as is well known, held the identity of gonorrhœa and syphilis—that gonorrhœa was produced by the same virus as syphilis. Resting, as this doctrine did, upon the production of syphilis in his own person by inoculation with gonorrhœal pus, it was widely accepted. One of two hypotheses, as Henry Lee writes ('Holmes's System of Surgery'), may be assumed in explanation of this result: (1) that the urethral pus was obtained from a syphilitic sore, alone and unmixed; (2) that it was

[1] 'Path. Soc. Trans.,' vols. xlii and xlv, Sir Felix Semon and myself.

mingled with the products of a co-existing gonorrhœa. That is, that in the particular case of "gonorrhœa" which Hunter was unlucky enough to select for this crucial and personal experiment, there happened to be a concealed urethral chancre; the infection was mixed, and of a kind analogous to the twofold infection with a soft sore and syphilis at the same or different sites.

One is tempted to reverse Morgagni's aphorism, "Non numerandæ sed perpendendæ sunt observationes." Everything depends here upon the number of observations, or rather their number constitutes their weight.

Were the rabbit in Dr. Lack's experiment the subject of primary uterine carcinoma, no essential relationship would, of course, exist between the scraping of the ovary and the appearance of the peritoneal growths. There is, however, another possible source of fallacy in a repetition of the experiment as planned by the author. Such an injury as that inflicted upon the ovary might be followed by a primary carcinoma of the ovary itself, not from the dislocation of normal epithelium into the ovarian tissue, but as the sequence of an infective process set up at the injured spot, and due either to the direct implantation of a *contagium vivum*, or to its indirect transference to it; and the carcinoma so arising might be the real source of a subsequent peritoneal infection. This possible source of error may be eliminated by adopting the method of intra-peritoneal injection, and I have recently carried out such a modification of Dr. Lack's experiment upon a series of rabbits. As the results of these will be recorded at a future date, their details need not be now given, except to state that scrapings of the ovaries of freshly killed rabbits were suspended in warm sterilised salt solution, and injected intra-peritoneally into a second set of animals.

In another series a similar suspension of testicle scrapings was injected; and in a third series a suspension of ovary and testicle scrapings combined. As a yet further modification, injections of such suspensions were made subcutaneously.

Let me now pass on to consider what collateral evidence is forthcoming in support of what may be designated the mechanical hypothesis of the origin of carcinoma, viz. that the mere traumatic dislocation of epithelium into a lymph space is itself sufficient to bring about the growth of a carcinoma.

The well-known dissemination of peritoneal papillomata which

takes place after the intra-peritoneal rupture, or spontaneous opening of a papilliferous ovarian cyst, does not really belong to this class of phenomena, seeing that such a cyst is distinctly a pathological new formation, and normal characters cannot be safely ascribed to the epithelium investing the intra-cystic growths. Similar papillomata are at times met with arising from the surface of one or both ovaries apart from the perforation of a papilliferous cyst; and doubtless their histological characters are in this case to be explained by their origin in connection with the columnar-celled germ epithelium which normally invests the ovary, and which, indeed, originally furnishes by its in-growth the lining of the true ovarian (as distinguished from Wolffian) cysts in which similar papillary formations may arise.

Such papillomata have the general features of contagious warts, and are comparable to those which arise in other positions. Setting aside the popular view as to the contagiousness of cutaneous warts, and for which there is some experimental evidence, the most interesting and striking proof of this is furnished by the papillomata occurring in the mouths of dogs. Not only is the contagiousness of such shown by the wide spread of the disease amongst dogs kennelled together (J. Penberthy, F.R.C.V.S.),[1] but Professor J. McFadyean and Mr. F. Hobday have proved the inoculability of these growths by experiments which have sufficient general interest to justify their citation.[2]

A series of four experiments were made. One such wart was excised from the buccal mucosa of the mouth of a young fox-hound, and its cut surface was used to rub a small area of lightly scarified mucous membrane on the right upper lip of each of three dogs, namely, a pug and two fox terriers. About a month afterwards a slight ridge of growth appeared at the site of inoculation. After attaining in the fox terrier a size and appearance almost identical with the natural warts in the mouth of the foxhound the tumours began to shrink, and eventually almost disappeared. The pug was killed with chloroform, and one of the experimental warts was cut off and rubbed against a small area of scarified mucosa on the left side of the upper lip of each of the fox terriers of the preceding experiment, and on both sides of the upper lip of a bull terrier. The attempts to reinfect the

[1] 'Journal of Comparative Pathology,' 1898, vol. xi, p. 363.

[2] Loc. cit., p. 341.

mouths of the two fox terriers were entirely negative in result, but on each side of the lip of the bull terrier papillomata formed at the scarified spot.

The spontaneous disappearance of cutaneous warts in the human subject is well known, and equally so amongst obstetricians is the retrogression of the disseminated papillomata of the peritoneum which follows removal of the ovaries bearing the primary growth. This latter phenomenon is one that has excited much surprise (a striking instance is cited by Dr. Cullingworth in the 'Obstetrical Transactions,' vol. xxxiv, p. 154), but, like the spontaneous disappearance of cutaneous or mucosal warts, it is possibly due to the acquirement of an immunity. The tumours, that is to say, may lead to their own disappearance, in consequence of the elaboration of some substance antidotal to the action of another produced within the growth, and without which the growth itself would not take place, the auto-immunisation being too feeble to effect a spontaneous disappearance of the whole, but enough to bring about that of the disseminated growths after the voluminous parent masses have been removed.

Some will contend that such disseminated papillomata have a limited term of life, and that once the parent tumour is removed no further formation takes place, since no further source of infection exists.

But against such an explanation is the obvious answer that the disseminated growths would in turn furnish a further series of centres wherewith to maintain the infection, even if they themselves eventually disappeared; just as the metastatic growths in sarcoma or carcinoma furnish a second series capable of producing yet a further. That contagious warts have a certain age limit, after which they retrogress, is shown by the spontaneous disappearance of the warts in the mouths of dogs (already referred to), and this after they may have attained extensive dimensions and a wide local distribution. But the fact does not carry its explanation with it, and does not solve the question why such a retrogression should take place.

Whether certain of the cases of spontaneously disappearing "sarcoma" in man may not come within the same class of phenomena is a speculation not unworthy of consideration.

The foregoing papillomata are instances of neoplasms arising from the transplantation of *abnormal* epithelium. But to turn to

the case of *normal* epithelium. The most recent work in this direction is that of Lubarsch and his pupils, Krückman and Lengemann.[1] Emulsions of various glandular organs were injected into the jugular vein of rabbits. No growth ensued in any part of the body as a result.

The list of organs used, though it comprises testicle, does not include ovary, a notable omission which needs making good. In another series of experiments small portions of glandular organs were mechanically detached and allowed to remain *in situ*, or implanted into the organs of other animals of the same kind. The fragments, even in cases where a small degree of growth ensued, before long shrank and disappeared. The history of tissue-fragments detached and displaced within a glandular organ by injury in the human subject must be assumed after these experiments to be similar in kind.

In the case of the injection experiments the vascular and not the lymphatic system, it is true, was chosen.

Yet that this does not weaken the argument appears in the metastasis which regularly occurs by way of the blood-stream in the course of sarcoma, and is not unknown in carcinoma, as exhibited in the secondary hepatic growths that may arise in connection with columnar-celled carcinoma of the intestinal canal or rectum, or in Sir James Paget's classical case of malignant "chondroma" of the testicle, which, as proved by the late Professor Kanthack and Mr. T. S. Pigg, was really a chondro-carcinoma infecting the lungs by way of the spermatic veins.

It follows as a corollary that, in order for an embolus to proceed to the growth of a tumour, some morbid character must be impressed upon the epithelium so transplanted.

It is, at present, a common practice amongst gynæcologists to examine both ovaries in every case of ovariotomy, and to incise or puncture any follicular cysts which present themselves in the otherwise sound gland that is left unremoved. This has been done by Dr. Cullingworth many times during the past few years. Yet though the ovary is simply surroundedwith aseptic sponge into which the fluid of the cyst is received, and is afterwards returned to the abdomen without any germicidal or cytocidal lavage, no instance of consequent peritoneal carcinoma has so far arisen.

[1] 'Geschwülsten und Infectionskrankheiten,' and in the 'Verhandlung der Deutschen pathologischen Gesellschaft,' 1899, p. 97.

But the epidermal cysts of the palm and palmar aspects of the fingers furnish, perhaps, the most instructive object-lesson of the results that follow the traumatic dislocation of normal epidermal cells into or beneath the corium, and one to which I referred on the occasion of Dr. Lack's bringing his experiment before the notice of the Medical Research Club in July of last year. I have had opportunities of examining three or four such cysts, and quite recently one which was removed by Mr. E. C. Stabb from the palm of a woman aged fifty, who three years previously had run a pin into the part; the wound bled, and a week or two afterwards a small swelling appeared which slowly increased in size.

The cyst, as now studied, lies altogether beneath, and separated by the fibrous tissue of the corium from, the general epidermis. Its lining has, as in other examples, all the characters of true epidermis, presenting most inwardly a thick laminated layer of horn, beneath this a well-pronounced stratum granulosum, and still more deeply a rete Malpighii with an upright series of cells set upon the fibrous tissue, which cells, though parallel, are somewhat displaced from the vertical as a result of the oblique incidence of pressure. The rete of the cyst has about the thickness of the general rete where this lies on the summits of the papillæ. The cyst has an ill-defined wall of fibrous tissue, not differentiated in its more superficial or uppermost part from that of the corium, and it is completely devoid of papillæ or glandular structures.

In the lower part of this cyst there occur areas where the deeper portion of the epidermis is invaded by leucocytes and multinuclear phagocytes, the epithelial elements being disparted and thrown into disorder by the inroads of the destroying cells. The destruction of necrotic epithelium by multinuclear giant-cells has been described in carcinoma by Deunschmann ('Journal of Pathology,' Nov., 1894), and by myself in a calcifying epithelial tumour ('Path. Soc. Trans.,' vol. xlviii, p. 224).

This invasion is to be associated, in the present case, with an inflammatory process, rather than taken as representing a normal removal of the implanted tissue after its having undergone a limited degree of hyperplasia. There was, Mr. Stabb tells me, the history of a subacute inflammatory attack, as shown by redness and increase of the swelling a week or so before its removal.

The contents were scanty, of milky consistence, and greyish white, containing epithelial *débris*.

Such cysts remain of small dimensions, the implanted tissue behaving in its after-growth much as in the experiments already cited.

After a certain amount of proliferation growth ceases, but though epithelial cells are here displaced into the lymph-spaces of connective tissue, no formation of a carcinoma ensues.

And amongst the same class of phenomena must be ranged the multiple formation of intra-abdominal cysts which may follow the rupture of an ovarian dermoid.[1]

In neither of these cases can it be objected that the epithelium is for some special reason incapable of furnishing a carcinomatous growth. Not only does the common form of cutaneous carcinoma arise from the deeper, actively growing stratum of the epidermis, but the lining of ovarian dermoids may, as is well known, become the source of a similar neoplasm. The one example of the latter occurrence which I have had occasion to examine was an oval cyst (now in the museum of St. Thomas's Hospital), five by three inches in its chief diameters; one end of this is capped at the site of the ovary with a concavo-convex new growth, an inch in extreme thickness, and two and a half in diameter.

Histologically the tumour is a typical keratinising squamous-celled carcinoma. The cyst was removed by Dr. Cullingworth in May, 1899, from a woman aged sixty-six, a widow, who had felt pain in the side four months, and noticed a swelling for six weeks. The growth was adherent to the bladder, but as found after death the vesical mucosa was everywhere normal and intact, proving that the carcinoma arose not from the bladder but the lining of the cyst. The cyst cavity contained a yellow fatty substance, which set on cooling, with intermingled hair. Death took place on June 2nd from intestinal obstruction.

The rupture of such a malignant cyst might lead to peritoneal metastasis; but in the case of simple ovarian dermoids rupture is followed by the production of circumscribed cysts as simple, and not by a carcinomatous infection of the peritoneum such as should arise were the mechanical hypothesis of the origin of carcinoma a true one. *January 16th*, 1900.

[1] 'Path. Soc. Trans.,' vol. l, p. 232, A. C. Latham.

10. *Pigmentation cirrhosis of the liver in a case of hæmochromatosis.*

By Maude E. Abbott, M.D.

The case which forms the subject of this paper was brought before the Montreal Branch of the British Medical Association in May, 1898, by Drs. Adami and Stewart, and a brief reference is made to it by the former in his article on "Cirrhosis" in Sajous's 'Annual and Analytical Cyclopædia.'(1) For reasons which it is unnecessary to give here a detailed description has been delayed until the present time.

I am indebted to Drs. Adami and Stewart for permission to report this rare condition, the first of its kind observed in America, and indeed the first of its kind recorded as occurring in the female. The latter I have to thank for the clinical history, and the former for the *post-mortem* notes, for access to the material, and for direction in its study throughout.

The case was one of cirrhosis associated with so-called hæmochromatosis, the "cirrhose pigmentaire" of the French school. An advanced cirrhosis of the liver and a moderate degree of chronic interstitial pancreatitis were associated with an extensive deposit of iron-containing pigment in the tissues. There was a bluish-grey slaty tinge to the skin, and a rusty brown discoloration of the internal organs. Sections of the liver and pancreas, and to a lesser degree of the spleen, supra-renals, and heart muscle, were loaded with golden brown pigment, which responded with a deep blue colour to Perl's test for iron.

The few cases that are analogous to this that are on record have of late years been the subject of much discussion among Continental writers. Indeed, the combined occurrence of hæmosiderosis and cirrhosis, and what is more, the very frequent combination of hæmosiderosis, cirrhosis, and diabetes, which is the more common, forming the "diabète bronzé" of French writers, invites inquiry, for the ætiology of the three conditions is alike obscure. Whether the one condition be dependent upon the other, or whether all are due to the action of one common cause,

there may lie in their co-existence some clue to a pathogenesis that is as yet incompletely understood.

Among English observers, up to the time that our own case occurred this subject had received little or no attention. Saundby, in his lectures on "Renal and Urinary Diseases,"(2) has a brief reference to one case of bronzed diabetes observed by him, while a case of a peculiar pigmentation of the skin described by Galloway (3) may be possibly another example of this condition. But further than this we have been unable to come across any reference either in English or American literature. Recently, however, the literature has been enriched by an article by E. L. Opie,(4) in which an able discussion of the subject is added to the report of a case occurring in the practice of Dr. T. Opie, of Baltimore. In this, and in a recent article by Anschütz,(5) the literature and the possible ætiology are so fully discussed that it will be necessary for us to do little more than add the few facts observed by us to those already upon record, although it will be seen that a study of these facts leads up to conclusions a little different from those reached by Opie.

Clinical history.—Mary G—, æt. 50, unmarried, was first admitted to the Royal Victoria Hospital under Dr. Stewart in July, 1897. Her present illness began two years previously with symptoms pointing to gastric irritation. Gastric pain and vomiting were complained of at intervals up to the time of her admission. For upwards of ten years she had been in the habit of taking an undiluted glass or two of gin daily. For some few months previous to her admission this gin had been replaced by beer. For years, also, she had been in the habit of drinking a mixture of vinegar and soda two or three times daily. She had a tuberculous family history, although she herself showed no signs of this disease.

On admission she was found poorly nourished, with yellowish conjunctivæ, while the face, neck, and hands presented a marked discoloration. The skin of these regions had a dark bluish or slaty colour. Similar changes, but less marked in degree, were present generally over the skin of the unexposed parts of the body.

There was visible pulsation in the superficial arteries, and a fairly well-marked degree of general arterio-sclerosis. At the

apex and over the aortic area a soft blowing systolic murmur was audible.

There were physical signs pointing to effusion into both pleural cavities, more marked on the right. She was troubled with cough, accompanied by the expectoration of scanty brown sputum, which under the microscope showed epithelial cells, granular material, and a few brownish flakes.

She complained of a sense of weight in the epigastrium, and frequently vomited after meals. A test breakfast showed the presence of hydrochloric and lactic acids, but not of butyric acid. The abdomen was fuller than normal, and in the epigastrium was a firm, hard mass having a rough and convex surface with well-defined borders. The movements of this mass during respiration were synchronous with those of the liver. The gall-bladder could not be palpated. The spleen was found considerably enlarged, reaching to within two and a half inches of the anterior superior spine.

A few weeks after admission she was transferred to the surgical department of the hospital for treatment of a suppurative otitis media and mastoid abscess. Upon her return to the medical side her general nutrition was found to be considerably improved, there being a definite gain in weight and strength. Pigmentation of the skin, however, was distinctly deeper in colour, although it varied somewhat from day to day. It was so marked that the patient was familiarly known throughout the hospital as "Blue Mary." It was of a deep ashy colour, deepest, as on admission, upon the exposed parts. Eventually some cyanosis of the lips, ears, and finger-nails showed themselves, together with a slight degree of subcutaneous œdema of the lower limbs. On several occasions the chest was aspirated and a few ounces of blood-stained serum removed. During her residence in the hospital epistaxis, although moderate in degree, was frequently complained of, and for some days previous to death much blood-stained fluid drained from the mouth.

The urine at no time presented abnormal characters, save on a few occasions there was a trace of albumen; sugar, although frequently tested for, was never found to be present.

On April 15th, 1898, the patient became suddenly worse, passing into a semi-stuporose state and refusing nourishment. She

died on the following day. Previous to this sudden and fatal attack her condition had varied little for two months, the discoloration of the skin had remained about the same, although varying in deepness of tint from day to day. The diagnosis made during life varied between malignant disease of the liver itself, or of the head of the pancreas becoming adherent to the liver, and of hepatic cirrhosis.

Pathological report.—The following is a brief abstract from the report of the autopsy, which was made eighteen hours after death.

The body was that of a well-nourished woman of middle age, the face and exposed parts of body were of a curious ashen grey to bluish colour, other parts were tinged and bluish grey, but to a less extent. The skin of the face was rough; that of the palms and hands singularly smooth and almost silky.

On opening the abdomen a characteristic pungent subacid odour, exhaled by the body in general, was given off very strongly. There was a complete absence of ascites. There were several bands of richly vascular omental adhesions to the parietes in the right anterior portion of the abdomen. The stomach was large, greatly distended, and of a slaty colour. The portions of the organs which were in contact with the stomach—the inner surface of the spleen, the under surface of the left lobe of the liver and the pancreas—showed an intense blue-black pigmentation, evidently *post-mortem*. The coils of the small intestines were full, and of the same slaty blue colour presented by the stomach. The edge of the liver passed to about 1·5 cm. below the ensiform cartilage, the right lobe being almost entirely covered by the ribs, the relatively large left lobe forming the main visible portion, and forming, further, the tumour visible during life; the visible surface was distinctly of the hobnailed type.

Upon removing the organs the stomach was found large, rather thin-walled, and contained abundant black blood and gas; the mucosa was stained black; there were no enlarged submucous veins of the stomach. The first few feet of the jejunum were greatly distended with bluish fluid blood. The lower portion of the small intestine was relatively empty, but blood-stained, to within a few feet of the valve, where again was more solid coagulated blood, which filled the colon right

down to the rectum; evidently the cause of death was this very excessive hæmorrhage.

On examining the œsophagus, it showed a plexus of dilated and varicose submucous veins, forming here and there well-marked projections of the mucosa. At a point not quite an inch above the cardiac orifice and roughly along the posterior median line of the œsophageal tube, pressure upon one of the projecting varicosities, led to free oozing of blood out of a little punctate depression of an ulcer. Here, evidently, was the seat of hæmorrhage.

The liver was of normal weight (1550 grammes, or about 51 oz.), but on the whole was rather smaller in dimensions than normal, the right lobe being relatively more shrunken than the left. There were extensive adhesions in the shape of well-formed vascular fibrous strands between the right lobe and the diaphragm; no evidence of gummata. On section the organ was dense and firm, presenting everywhere small lobular islands of dirty yellowish colour surrounded by bluish grey; glistening fibrous tissue present in great abundance. The reverse of the usual colour relationships between the interstitial tissue and the parenchyma was a prominent feature.

The spleen was relatively enormous, weight 720 grammes, and in dimensions 23·5 × 13·5 × 4 cm. There were numerous adhesions to the diaphragm and surrounding organs, which broke down easily. The organ was flabby, and on section was pale and pulpy.

The pancreas was long, thin, and moderately congested. The supra-renals were of dark colour with softened medulla.

The kidneys presented a condition of mixed nephritis, and were relatively large and somewhat congested.

The bladder and vagina were normal; the uterus atrophied.

Histology.

(Sections stained with eosin-hæmatoxylin by van Gieson's method.)

The liver.—Under a low power (Reichert No. 3) two pathological changes are most strikingly apparent: an extensive annular cirrhosis with atrophy of the liver cells, and a heavy

golden brown pigmentation of both parenchyma and fibrous tissue.

Connective tissue.—Wide bands of fibrous tissue traverse the section irregularly, sometimes leaving two or three lobules intact, more often invading the parenchyma, penetrating some lobules, and obliterating or alterating the shape of others. So enormous is the cirrhotic change that sometimes the whole field of the microscope is occupied by an area in which no hepatic tissue is visible. The central vein lies sometimes free in the lobule, sometimes it is the centre of a localised area of fibrosis, and, most often, it is involved in the wide stretches of cirrhotic tissue that occur. At points where diverging bands of tissue meet, or again where new tissue is invading the parenchyma, heavy clumps and masses of dark brown pigment occur. The fibrous tissue is in parts of old standing, poor in cells; in other parts, generally in the neighbourhood of the degenerating hepatic tissue, or where it itself is most heavily pigmented, it is very cellular. It is very vascular, the numerous thin-walled vessels filled with blood giving it in some places an almost angiomatous appearance; a moderate number of new bile canaliculi occur.

The hepatic parenchyma.—Little lobular arrangement remains. The liver cells are often atrophied, especially those that are deeply pigmented, or those lying in the neighbourhood of the cirrhotic bands. No sign of compensatory hypertrophy is seen. Almost all cells show a greater or less degree of pigmentation, which gives them under this power a diffuse golden brown colour much lighter than that of the heavy brown masses lying in the connective tissue. Those cells lying at the periphery are generally most heavily pigmented, but sometimes the change extends quite evenly to the very centre of the lobule. In some parts of the section there was slight fatty degeneration. With a higher power (Reichert No. 7 *a*) the form and arrangement of the pigment is very interesting. It is of two kinds: very fine granules, and coarse highly refractive particles which are generally rounded, and often resemble red blood-corpuscles both in form and size: these particles are aggregated in the fibrous tissue into heavy clumps and masses. In the older, less cellular regions pigmentation is scanty, the granules being generally small, and arranged along the course of the fibres. In the newer, more cellular part, where the pigment is abundant, it is

quite irregular both in form and arrangement, fine granules, coarse particles, and heavy masses lying between the cells and fibres, or apparently free upon their surface. The pigment does not appear to lie within the connective-tissue cells. Highly pigmented liver cells are seen enclosed in the connective tissue. They are sometimes completely transformed into a mass of pigment granules, and are recognisable only as the remains of liver cells from their form and nucleus, which, though staining badly, can still be made out.

The heavy homogeneous pigment masses in the connective tissue also often resemble liver cells in form, and some peculiar spindle-shaped cells occur, which from their segmented arrangement upon each other suggest an origin from the parenchyma. These collections of cells bear a general resemblance to fibroblasts, but the transverse segmentation is distinct from anything ever seen in cells of connective-tissue origin. I would suggest that collections of cells of this nature led (or misled ?) Hamilton to conclude that the liver cells can function as fibroblasts in the cirrhosed liver.

The endothelium of capillaries and of portal vessels is often pigmented. The epithelium of the new bile canaliculi is generally free from pigment. This is the opposite to what has been observed in most cases reported, and of the condition we have ourselves seen in the livers of two cases reported by Kretz, (7) which we have had the opportunity of examining.[1]

In the liver cells the pigment, when in moderate amount, is finely granular, and is arranged along the side of the cells bordering upon the bile capillary and around the nucleus. When the cell is loaded the granules are coarser, sometimes angular in form, and there is no regular arrangement. When pigmentation has gone on to destruction of the cell quite large particles occur, generally rounded. The variation in size and appearance indicates a gradual clumping of the finer granules into larger more refractive masses. Here and there through the parenchyma occur islands of such broken-down cells, represented by coarse golden brown granules, among which young connective-tissue cells are developing. In most instances of extreme pig-

[1] I have to thank Dr. Augenette Parry of New York for her kindness in having forwarded to me this material, which she obtained through the courtesy of Dr. Kretz and Prof. Albrecht of Vienna.

mentary degeneration, unless the cell be completely broken down, the nucleus still stains well. In the endothelium of the capillaries and in the leucocytes granules were observed; none were seen free in the blood-stream.

When the liver was tested microscopically for iron by Perl's test, the whole section assumed a deep blue colour. Microscopically all pigment granules had taken on a Prussian blue colour; the heavy clumps in the connective tissue are almost black, while the finer particles in the liver cells are a brilliant blue, or sometimes a bluish green.

Pancreas.—Here again, as in the liver, there is overgrowth of connective tissue and extensive pigmentation. Trabeculæ penetrate the parenchyma, sending finer prolongations inward which surround the acini or groups of acini. The new tissue seems to be of slower growth than that in the liver, for it is much less cellular; it is also less vascular. Clumps and masses of pigment lie in it identical in form and appearance with those in the cirrhotic areas in the liver. Within the fibrous tissue islands of one or more degenerating acini often occur, many cells of which have lost their form, and have become simply a mass of pigment granules.

The epithelial cells are irregularly, often heavily pigmented, and there is extensive necrosis. Examined under an immersion lens of high magnification, where the fine granules both in the hepatic and pancreatic cells are relatively scattered and separate, they are seen to be arranged with remarkable persistence in pairs, and thus closely resemble, if they are not identical with, the diplococcoid forms in the liver and other cells to which Professor Adami has called attention.

Retro-peritoneal lymph-glands.—The only lymph-glands examined were from the neighbourhood of the pancreas; the fibrous septa were distinctly widened, but did not seem to penetrate into the lymphoid masses lying in their meshes. Part of the gland was comparatively free from pigment; here and there a few round particles lay between the cells, and sometimes a row of fine granules surrounded the nucleus, as though enclosed within the cell protoplasm. A large area of the gland was on the other hand completely transformed into coarse granules of golden brown pigment, between which lay isolated lymphoid cells. In these areas there seemed to be no increase of connective tissue.

At points where the pigmentation was heaviest there were areas of necrosis, hyaline regions staining with hæmatoxylin-eosin a pale pinkish violet, in which lay a curious network of highly refractive homogeneous fibrils. This network was of a pale yellow colour in unstained specimens, and did not stain with hæmatoxylin and eosin. With van Gieson's stain the fibrils took a dark greyish, almost black colour, they gave a deep Prussian blue with Perl's test, the blue colour developing here much more rapidly than in the other pigmented areas of the section. The iron reaction appeared after ten minutes in a 1 per cent. solution of *cold* hydrochloric acid.

These curious fibrils resemble nothing ever observed by us before; their general appearance strongly suggests a capillary network which has undergone hyaline degeneration and has taken up iron pigment in a soluble form.

The spleen.—The trabeculæ did not appear to be increased. By van Gieson's method a limited fibrosis is apparent near the surface of the organ, fine threads of fibrous tissue traversing the parenchyma. Pigmentation is scanty, some very fine granules being scattered through the tissue. These do not react to Perl's test, although the whole section takes on a pale diffuse blue colour. The only true Prussian blue reaction that occurs is in the adventitia of the large vessels in which the coarsely granular form of pigment lies.

Heart muscle.—Van Gieson's method shows a very early fibrosis, fine strands of connective tissue running here and there between the fibres. There is limited pigmentation, golden brown finely granular pigment being arranged around the poles of nuclei, as in brown atrophy. The reaction to Perl's is irregular; in some cells the granules react freely, in others the colour remains unchanged; the whole section takes on a diffuse blue tinge.

The supra-renals.—There was extensive necrosis of the medulla (probably *post-mortem*), and a brownish pigmentation which gave no iron reaction. There were scattered areas of small-celled infiltration in the medulla, and dense iron pigmentation of the epithelium of some of the cortical acini.

The kidney.—Some congestion and a mixed nephritis exist. There was no fibrosis and no iron pigmentation except in the epithelium of a few isolated tubules in the cortex.

The lungs.—With the exception of a few leucocytes lying free in the alveoli, which took a diffuse blue tinge, no iron was apparent.

The skin.—In spite of the peculiar bluish-grey slaty tinge described, there was surprisingly little microscopical evidence of pigment. All that was observed was a few golden brown granules in some large irregularly shaped cells situated in the connective tissue of the dermis a little below the Malpighian layer; there was no reaction to Perl's test. The discrepancy between the macroscopic and microscopic appearance of the skin is noted by other students of this disease, and it has been suggested that the discoloration is simply due to a peculiar form of cachexia.

Unfortunately the only part of the alimentary tract reserved for microscopical examination was the lower part of the œsophagus and the cardiac end of the stomach; the wall of the latter turned a diffuse blue with Perl's test; the muscle cells of the muscularis mucosa contained granules of golden brown pigment, not reacting to Perl. The lymphoid follicles in the subserous layer of the stomach were transformed into dense masses of golden brown pigment, in which lay areas of necrosis showing the same highly refractive fibrillary network observed in the retro-peritoneal glands.

As indicated by the *post-mortem* blackening of the organs in the immediate neighbourhood of the stomach, early putrefactive changes had occurred, with diffusion of hæmoglobin from the blood abundantly present in the viscus. The diffuse reaction of the whole stomach wall may thus be regarded but as an evidence of this diffusion.

The histological study of this case revealed the following points:

1. More or less fibrosis of all organs except the kidney was associated with a greater or less degree of hæmosiderosis.

2. In both liver and pancreas the heavy pigmentation of the connective tissue had its source, in part at least, in the broken-down pigmented cells of the parenchyma.

3. A fairly advanced chronic interstitial pancreatitis existed without the clinical picture of diabetes so common in cases of advanced hæmochromatosis.

A word with regard to the micro-chemical reaction:

Sections of the organs were tested with ammonium sulphide and with potassium ferri-cyanide, with affirmative results. In the closer study of the case, however, Perl's test only was used. In its employment several difficulties were encountered.

The routine method at first employed was as follows: potassium ferro-cyanide, 2 per cent. solution, three minutes; hydrochloric acid, 1 per cent. watery solution, two to five minutes; washed with distilled water.

The bulk of the material was hardened in Müller's fluid to which 2 per cent. formalin had been added, and was preserved in methylated spirits. On taking up the study of the case when the material was some two months old, the writer found that whereas the iron reaction had been prompt in the fresh specimens examined shortly after the autopsy, no typical reaction now occurred, the granules turning a greenish yellow, or at most a green colour, many not reacting at all. The only part of the tissue where the Prussian blue colour developed after ten minutes in cold hydrochloric acid was the remarkable hyaline network seen in certain of the necrotic areas of the lymph-glands.

It was at first thought that the formalin and the fixing fluid had liberated the iron, or else had thrown it into closer combination. That the iron was not liberated, but that the reaction was only delayed, was proved by the fact that sections left in hydrochloric solution two to twenty-four hours gave a typical Prussian blue colour, while when the test was performed with hot hydrochloric acid the reaction was almost instantaneous.

Pieces of liver were placed for four days in 4 per cent. formalin, cut and tested with control parallel sections of the Müller-formalin material. The sections kept in formalin gave a typical reaction in two minutes with cold hydrochloric acid. Thus the action of the formalin was to throw the iron into looser combination and make it react more readily.

Tissue hardened from the first in alcohol reacted readily. Müller's fluid would thus seem to have been the cause of the delayed iron reaction. Quincke,(8) in his work on hæmosiderosis, made a similar note to the effect that Müller's fluid interferes with the iron reaction.

It is noteworthy that the iron-containing pigment reacts very unevenly to Perl's test; many granules showing at most only a

light yellowish green at the end of twenty minutes in cold HCl assume at once a deep blue colour on being placed in the hot acid. In the lymphatic gland, after five minutes in cold HCl only the curious homogeneous network reacted, while on treatment with hot HCl all the golden brown granular pigment turned a deep Prussian blue.

The obvious conclusion is that in our case all the granules, both the darker brown and the paler yellow, in the liver, the lymphatic glands, and the pancreas, *i. e.* both the hæmosiderin, and what we regarded as the hæmofuscin of other observers, are iron-containing, the essential difference being that in the one the iron is in looser, in the other somewhat firmer combination, only being rendered free by the action of hot HCl; on the other hand, even hot HCl, as employed by me, did not cause the reaction to develop in the "hæmofuscin" granules of the muscle cells.

A point of interest in this case is the occurrence of a chronic interstitial pancreatitis without any diabetes. Diabetes has been so commonly associated with cases of advanced hæmochromatosis that it has been regarded by many observers, especially in France, as a distinct morbid entity. The first cases reported were published by Hanot and Chauffard,(9) 1882, under the name of "diabète bronzé." The diabetes would seem to be secondary, dependent upon disease of the pancreas, which has been found affected in every instance in which microscopical examination has been made. Anschütz (10) has collected twenty-four cases of diabète bronzé from the literature. In eighteen cases there had been microscopical examination; there was chronic interstitial pancreatitis fifteen times, and three times a heavy deposit of iron pigment in the glandular epithelium.

In our case, however, as in several others in the literature (as, for instance, one of Hintze's [11] and in Opie's), there was pancreatitis without diabetes; in other words, a condition anatomically of the same order as diabète bronzé existed without the clinical features of the disease. It is possible that, as suggested by Opie, the disease of the pancreas may not have been sufficiently advanced to give rise to symptoms, enough of the gland remaining healthy still to perform its functions. Or the diabetes may have been latent while the patient was under observation.

Marie (12) notes a tendency in these cases for the diabetes to disappear under treatment, or in the later cachectic stages of the disease, and in six of the cases collected by Anschütz this occurred. At all events, cases such as these seem to form a connecting link between the cirrhose pigmentaire, pure and simple, and the diabète bronzé of the French school, and would seem to indicate that these two conditions are not separate morbid entities, but stages in the course of one general disease.

The majority of cases of advanced generalised hæmochromatosis, with or without diabetes, seem to have been observed in France, and, as has been said, have been described by French writers as cases of bronzed diabetes or pigmentation cirrhosis. In Germany, on the other hand, where the cases have been fewer, the subject seems from the first to have been viewed from a wider standpoint, to which the later French writers are inclining. All cases in which there is an abnormal deposit of blood-pigment in the tissues have been classed together as different stages in the same pathological process, to which in 1889 von Recklinghausen gave the name of "hæmochromatosis." The most important studies along these lines are those of Quincke (1880), von Recklinghausen (13) (1889), Hintze (1895), and Kretz (1896).

Among ten miscellaneous cases, in most of which the iron pigment is confined to the liver cells and to the spleen, Quincke includes a case of general hæmochromatosis in diabetes. Von Recklinghausen included under the term hæmochromatosis cases of pigmentation cirrhosis and diabète bronzé, with others in which the pigmentation was limited to the intestinal wall alone. Hintze gives six cases, in two of which there was general hæmochromatosis without diabetes, in one pigmentation confined chiefly to the liver and spleen, in one affecting only the pancreas and retro-peritoneal glands, and in two involving the intestinal wall alone.

Kretz, in his valuable monograph on hæmosiderin and cirrhosis, in a study of some eighty-eight livers obtained the following results:—In twenty-six cases of cirrhosis of the liver there was hæmosiderosis fourteen times; in two instances these were cases of diabète bronzé; in four other cases, typhoid, pneumonia, chronic tuberculosis with hæmorrhagic pleuritis, and chronic peritonitis with marasmus, there was a moderate deposit of iron pigment in the liver cells not extending to the connective tissue.

In the microscopical study of sections of the liver and pancreas from the material before me—my own and the two cases of Kretz—I have noted repeatedly the heavily pigmented hepatic cells breaking down to form masses of coarse granular pigment in the fibrous tissue, which at such points is very cellular, evidently of new formation. This appearance would indicate that the formation of pigment is, in part at least, antecedent to the cirrhotic change. Other observers, Opie, Anschütz, Hintze, and Kretz, and, indeed, all whose work I have followed carefully, have noticed this appearance and drawn this conclusion.

If, then, the pigmentation be primary, it seems rational in studying the ætiology of this condition to follow along German lines, and seek to ascertain the pathological conditions under which pigment giving the iron reaction is deposited in the parenchymatous cell.

Following Kretz's example, I have examined micro-chemically the organs from a large number of cases. The following results are interesting:

Among sixteen cases of cirrhosis, there was hæmosiderosis six times. Here the liver only was examined, as the material was obtained from a number of cirrhotic livers collected for another purpose. In three of these cases pigmentation was marked, the iron being present not only as fine granules in the liver cells, but lying also in coarser masses in the connective tissue, as in our case of general hæmochromatosis. In the remaining three cases it was confined to the liver cells, lying as fine granules along the margin of the bile capillaries.

Among eight cases of typhoid examined there was hæmosiderosis twice: in one it was very slight, simply giving a greenish tinge to the section; in the second, in which there was a clinical history of intestinal hæmorrhage, it was marked, occurring in fine granules in the liver cells. The connective tissue was free.

Forty-one cases were chosen from the *post-mortem* material at the Royal Victoria Hospital of the past eighteen months, because there was a note in the report that golden brown pigmentation of the liver cells existed. The liver, spleen, pancreas, and sometimes the heart muscle, were examined. Cases of pernicious anæmia, where hæmosiderosis of the liver cells is an almost constant condition, were excluded. In these forty-one cases there was hæmosiderosis four times; both liver and spleen gave

a marked reaction, but the *pancreas was free from pigment in all cases.* In the liver the pigment lay in finely granular form in the cells, sometimes in the capillaries and the capillary endothelium, never in the connective tissue. In the spleen there was a diffuse staining, and also a coarsely granular pigmentation of the parenchyma. The trabeculæ were generally free. In a fifth case there was iron pigment in the capillary walls and contents, none in the liver cells or spleen. The following is a short account of these cases.

CASE 1 (Path. No. 41, 1898).—Male æt. 43. Scirrhous carcinoma of pancreas; secondary carcinoma of left lung, pericardium, and œsophagus; pericarditis adhæsiva; old empyema of left lung *forming an abscess cavity,* which had been operated on and drained; *venous congestion of the intestinal wall;* firm old adhesions between ascending transverse colon, omentum, and wall of gall-bladder.

Microscopical.—Liver.—Some small-celled infiltration along the portal sheaths, small cells scattered irregularly between the liver cells; pigmentation and fatty degeneration of the liver cells. With Perl's test the section assumes a diffuse blue colour, fine iron pigment granules lie in the cells, generally centrally in the acini along the margins of the bile capillaries. *No iron in the portal tissue.*

Spleen.—Some congestion and hyperplasia of the follicles. Coarse lumps and granules of iron-containing pigment giving an intense reaction to Perl are scattered through the parenchyma. Trabeculæ free from pigment.

Pancreas.—No pigmentation.

CASE 2 (Path. No. 1, 1899).—Old man. Pneumonia senilis; *large sloughing ulcer covering the whole surface of left leg;* skin over the surface of the right leg pigmented; inguinal glands enlarged; left sero-fibrinous pleurisy; *duodenitis;* brown atrophy of heart.

Microscopical.—Liver.—Heavy golden brown pigmentation in the cells; no marked increase of portal tissue, but areas of small-celled infiltration are scattered throughout the parenchyma, generally coinciding with the more heavily pigmented areas. Some newly formed bile-ducts lie in the portal sheaths. Liver

cells at the periphery of the lobules are most heavily pigmented; all the granules react strongly to Perl. In the blood-vessels are some small round bodies the size of a red blood-corpuscle which react deeply. *The connective tissue is free from iron.*

Spleen.—Marked congestion; some atrophy of parenchyma, with increase in size of trabeculæ. With Perl there is a diffuse somewhat blotchy blue staining of the parenchyma, in which coarse granules and masses of iron pigment lie free. Trabeculæ free.

CASE 3 (Path. No. 3, 1899).—Male aged 57. Operation five days *ante mortem* for irreducible hernia of ten days' standing; death from intestinal obstruction.

Post-mortem.—Double pneumonia; inflammatory infiltration and hæmorrhagic condition of great omentum, forming a mass to which the small intestine was attached, causing a kink which formed the point of obstruction. The whole of the *intestine* here *showed marked inflammatory change,* and the mucosa was covered with a necrotic pseudo-membrane.

Microscopical.—Liver.—Fatty degeneration and finely granular pigmentation of the liver cells, which are much atrophied and misshapen, and often broken down. No attempt at the formation of new connective tissue. Some congestion, the capillaries being often distended. Pigment in the liver cells reacts to Perl.

Spleen.—Congestion; some fibrosis; well-marked siderosis of parenchyma.

CASE 4 (Path. No. 8, 1899).—Male aged 76. Compression myelitis due to pressure from a large cancerous mass in the pelvis. Adeno-carcinoma of prostate and retro-peritoneal glands. *Large sloughing bedsore over sacrum* of about one month's duration.

Microscopical.—Liver.—Extreme fatty degeneration, almost the whole tissue being in parts transformed into a mass of fat globules; the remaining liver cells are often heavily pigmented. Some increase of connective tissue in portal sheaths. In this case the golden brown pigment in the cells does not react to Perl. Numerous dark granules lie in the leucocytes, in the

capillaries, and the lining endothelium of the capillaries, and stain a diffuse blue.

Neither spleen nor pancreas contains iron.

CASE 5 (Path. No. 20, 1899).—Female aged 69. Pneumonia; intestinal hæmorrhage on day of death.

Microscopical.—Liver.—Fatty degeneration of the liver cells, which are often swollen. There is finely granular iron pigment in the liver cells arranged along the walls of the bile capillaries; also diffuse staining of the capillary endothelium, as in the last case. Many leucocytes in the capillaries contain iron granules.

Spleen.—The parenchyma takes a diffuse blue tinge with Perl's method, and coarsely granular iron-containing pigment is scattered through it.

Pancreas.—No pigmentation.

There was in all these cases a history of localised blood disintegration, either hæmorrhage or chronic suppuration, and in all cases a history of some intestinal disturbance.

Blood disintegration, either from localised extravasations into the body tissues, or from breaking down of red corpuscles within the blood-stream—as in pernicious anæmia and extreme cachexias—seems to be very frequent in cases of hæmochromatosis. In Hintze's three cases there was a history of subcutaneous hæmorrhage, hæmorrhagic pericarditis, and hæmorrhagic peritonitis. Hindenlang (14) (1880) gives a case of advanced hæmochromatosis with cirrhosis occurring in the course of purpura. In our own case, though there was no obvious anæmia (no blood count was made), it is interesting to recall the tendency towards hæmorrhage evinced by the frequent epistaxis. On the other hand such a history is not constant, and blood disintegration may exist both as an extravasation and in advanced cachexias without hæmosiderosis of the liver cells. Zaleski gives a case of purpura in which there was no hæmosiderosis; I have myself examined several cases in which hæmorrhages had taken place into the tissues—among others a case of purpura—with a negative result.

Auscher and Lapique (15) injected blood into the peritoneal cavity of animals, and obtained iron pigmentation of the spleen, but not of the liver cells.

Hæmorrhage alone is thus clearly not the cause of hæmochromatosis; there must be something behind or accompanying it, a something which becomes active either under repeated interstitial hæmorrhages, or destructive changes occurring in the circulating blood. And further, it may be that some disturbance of the specific cells of the liver and other organs is also required to favour the deposit within them of the iron-containing pigment. We know, indeed, that under ordinary conditions the blood-pigment is eliminated in a soluble form, leaving no trace of its presence within the cells.

The remarkable frequency with which hæmosiderosis occurs in cases of cirrhosis and when affecting the pancreas, its frequent association with advanced disease of this organ, shows that this possibility must be kept in mind. Thus Kretz found hæmosiderosis in fourteen of the twenty-six, and we ourselves in six out of sixteen cirrhotic livers. On the other hand, the tissue changes in cirrhosis and the interstitial pancreatitis may themselves be due to the action of one common and primary cause, and there may be one common factor causing blood destruction, the liability to hæmorrhage and to morbid disturbance in the liver, pancreas, lymphatic glands, etc.; we cannot, I think, wholly pass over this possibility.

What has struck me is that common to all these cases we have evidence of more or less chronic intestinal disturbance. Indeed, as Hintze points out, the earliest stage of recognisable hæmochromatosis is that in which the walls of the small intestine are involved. We are forced also to recognise that in ordinary portal cirrhosis we have a similar history of chronic intestinal disturbance. Boix (17) has gone further, and has caused advanced cirrhosis in animals by feeding them with large quantities of the more deleterious products of intestinal digestion, and again by inoculating them with toxines developed from the bacteria inhabiting the intestinal tract. There is, then, a certain amount of possibility that the cause of hæmochromatosis is to be found in association with intestinal disturbance.

In cases Nos. 1, 2, 3, and 5 (Case 4, where the iron was only in the capillaries, may be omitted from consideration), and in the case of typhoid above mentioned, we found that the distribution of iron pigment differs from the case of general hæmochromatosis which forms the subject of this paper in the following points:

1. In the liver the pigment is found in the hepatic cell, where it lies in rows of fine granules along the margins of the bile capillaries; the connective tissue is free.

2. While there is pigmentation of both liver and spleen, the pancreas is quite iron-free.

An identical distribution of iron pigment occurs in many cases in the literature where there has been a history of local hæmorrhage.

The question arises, Is this a difference of degree only? or is it essential? In other words, Is hæmochromatosis a distinct morbid entity? or is it simply a more advanced stage in the same pathological process at work in the cases of more localised iron pigmentation cited above?

The pigmentation of the connective tissue does seem to be a further step in the same process. In these slighter cases the pigment granules lie along the margin of the bile capillary, apparently being continuously excreted. In pigmentation cirrhosis, while the same appearance exists in the healthier cells, there are large areas of extensive pigmentation where the cell becomes overloaded, breaks down, and forms a mass of coarse pigment lying free in the newly-formed connective tissue. The liver cell seems to have become unequal to its task of throwing off the insoluble granules which have been deposited in it, and succumbs at last to the accumulation of unrejected pigment which loads it down. Again, in the cases of cirrhosis where there was hæmosiderosis of the liver cell without general hæmochromatosis, the connective tissue is often pigmented, as in ten out of Kretz's fourteen cases, and in three out of our six.

On the other hand, the different distribution of iron in the organs seems at first sight to indicate that an essentially different process is at work. Not only in the one set of cases is the spleen pigmented, while the pancreas remains free; in the other pigmentation cirrhosis the pancreas with the other glandular organs is loaded with pigment, while the spleen is relatively free. A possible explanation may be that the degenerating liver cells have lost much of their power of excretion, and, ceasing to act as a natural barrier, allow the blood-pigment to pass on to the other organs. But this can hardly hold, for the lung is free from iron, while the pigmentation of the spleen is relatively slight. Neither those organs within the portal circulation, nor those lying in a

relation of contiguity with the liver, share evenly in the pigmentation, but certain elements which lie far removed from each other—for instance, the pancreas, thyroid, salivary glands, hypophysis cerebri, and heart muscle. These are all organs in which iron-free pigment is commonly formed. There would seem to be some degeneration of the parenchymatous cells of these organs, by which they become unable to throw off the altered blood-pigment deposited in them.

From the comparison of these cases and a study of the literature, the following conclusions are suggested:

1. In general hæmochromatosis some primitive agency, as yet unknown, is at work leading to—

   (*a*) An increased destruction of hæmoglobin taking place, either in localised hæmorrhages, or within the blood-stream, or perhaps sometimes within the parenchymatous cells themselves.

   (*b*) A degeneration of the cells of certain organs by which they become unable to throw off the granular pigment deposited in them, and, becoming loaded, finally disintegrate.

2. The cirrhosis would seem to be of the nature of a chronic interstitial inflammation, secondary upon the presence in the tissues of pigment set free after the destruction of the parenchymatous cell.

These are practically the conclusions to which Kretz came in his study along the same lines.

Hæmosiderosis of the liver cell was observed in our cases (as in many in the literature) to be associated with a history of intestinal disturbance, and at times (in three instances) of prolonged suppuration.

These facts suggest that the primitive agency, leading alike to blood destruction and to cell degeneration, may be bacterial in its nature.

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February 20th, 1900.

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11. *Some results of experiments with the toxins of the pneumococcus.*

By A. G. Auld, M.D.

The following remarks briefly embody some of the main results of an investigation extending over two years, and one in which nearly two hundred animals have been experimented upon.

Finding the published results of those who had experimented with regard to immunisation against the pneumococcus to be extremely diverse, and even in many points contradictory, the author carried out, in the first place, a prolonged series of experiments on the production and action of the toxins formed by the organism. In a previous paper[1] he pointed out that in broth the pneumococcus quickly produced lactic acid, which apparently inhibited its further growth. To counteract this, (1) some precipitated chalk—sufficient to form a thin layer at the bottom of

[1] 'British Medical Journal,' March 27th, 1897, p. 775.

the flask—was sterilised with the beef broth. The other media used were (2) decalcified broth, together with 5 to 10 per cent. sterile horse's blood plasma; (3) ordinary broth with 5 to 10 per cent. red layer of horse's blood; (4) ordinary broth with 10 per cent. Loeffler's serum; (5) broth with plasma and corpuscles combined.

1. First these media were inoculated with cocci from the blood of rabbits infected with pneumococci derived from the human subject. After two to five days' growth the cultures were filtered, and varying quantities of the toxins (2 to 20 c.c.) injected subcutaneously, and also into the peritoneum of rabbits. The result of injecting 10 to 20 c.c. was merely a slight and transient elevation of the temperature.

2. The same toxins were again injected into a number of rabbits, beginning with 2 to 5 c.c. and gradually increasing the dose to 15 c.c. These injections were made twice a week, until by the fourth week 40 or 50 c.c. had been administered. During this time the animals gained considerably in weight. To others larger doses, both subcutaneous and intra-venous, were given, 10 to 20 c.c. at an injection, until 50 to 60 c.c. had been reached. In some of these the weights fell after about a week, then in the course of another week or so the weights would begin to rise again. In one animal injected with the blood-broth toxin the weight fell 300 grammes, by the eighth day it gained 50 grammes and then remained stationary for twenty days, when a complete paralysis of the extensors of the legs set in. The animal became very ill, temperature 104°, hair rough, and it seemed about to die. It continued ill for many weeks, but slowly recovered from the paralysis, until in about three months it appeared well again. All the animals, together with two controls, were tested with living pneumococci four weeks after the last injection (except in the case of the paralysed one). The day after inoculation all except three and the controls were dead. On the third day all except one of the controls were dead; on the fourth day this control was dead. After the paralysed rabbit had completely recovered, it and a control were tested with virus. Next day the paralysis had returned exactly as before. Two days afterwards it died, the control surviving it by about eighteen hours.

3. The organism was carried over in rabbits to three generations, when its virulence was much increased. [The cultures

were preserved in blood in sealed glass bulbs at the ordinary room temperature.] After four days' growth in the same media the toxins were filtered off and injections made as before. The results were again disappointing, even when doses of 30 c.c. were employed. A curious effect of the toxins began to come out, namely, that sometimes the animal somewhat suddenly died after two to four weeks or longer without showing any signs of previous illness, and without any discoverable *post-mortem* changes.

4. The culture was carried over by inoculation into the pleural cavities of rabbits for six generations. It then became intensely virulent, so much so that a single small loopful of the infected blood killed in eight hours without producing any local lesion, the blood teeming with capsulated cocci. Finding the media somewhat disappointing, the author confined the cultivations to veal broth with chalk, and veal broth with 20 per cent. horse's serum. This highly virulent organism grew very richly. It continued growing for ten days, forming a thick deposit, and also numerous large flakes and strings suspended in the medium. After a fortnight it was filtered. The results of injecting this toxin were as follows :—In doses of 10 to 20 c.c. an illness was induced with rise of temperature, from which the animals recovered, the serum toxin producing the stronger effect. In doses of 30 c.c. there ensued illness with a high temperature (104° to 106°), loss of weight, and generally death from the tenth to the fourteenth day. When the toxin was heated for an hour at 65° C. the effect seemed to be distinctly more marked. In these cases, also, diarrhœa was a not uncommon feature. This dose proved fatal to animals weighing 2700 grammes. Experiments were also made with this serum toxin with a view to immunising. Graduated doses were given up to 30 c.c., and also moderate doses subcutaneously. The animals were tested with virus at varying periods from the twenty-first to fifty-seventh days. In all cases they succumbed before the controls. From the fiftieth to sixtieth days some of the animals were again treated with large doses of serum toxin. They showed increased susceptibility to its action, and in one case fore-leg paralysis supervened, as was found in a former case. They were also treated with virus of medium strength, together with a control. A local hard swelling formed at the site of inocula-

tion in the abdomen. They all died within a week, except the control, in whom the swelling turned into an abscess discharging pus externally. It ultimately recovered.

5. The broth was again modified by the addition of a considerable quantity of blood obtained from rabbits infected with the virulent organism. The lethal dose was in this case also about 30 c.c. to animals weighing from 2500 to 3000 grammes, but it was found impossible to measure this accurately, as the animals showed slightly different degrees of susceptibility. Injections were again made in graduated and also in large doses. The animals were subjected to virus at varying periods from the fourteenth to twenty-seventh day. In every case death occurred sooner than in the controls.

6. The toxin was injected in very small and gradually increasing doses, beginning with $\frac{1}{2}$ c.c. subcutaneously, increasing by $\frac{1}{2}$ c.c. every third day until the twelfth day, then 2 c.c. and so on, until the dose reached 10 c.c. One or two of the animals died quite suddenly during this period—a circumstance already alluded to. All the others gained in weight. They were tested by virus at varying periods from the twenty-first to the forty-second day. The result was the same as in the others —they succumbed before the controls. It should be mentioned that the organism was grown by Dr. Cartwright Wood in veal broth rendered considerably alkaline, being standardised in this respect with phenol-phthalein, for the purpose of serving as a medium for the diphtheria bacillus. Growth occurred extremely well in this medium, and the results of a limited trial were not very materially different from those produced by the serum toxin. The most notable result of these experiments was undoubtedly the increased sensitiveness to the pneumococcus produced by inoculation of its toxins—in rabbits at least. Under all circumstances of dosage this super-sensitiveness was manifest, and, consequently, any attempts to immunise in this way seemed to be contra-indicated, unless some other method of administering the toxins happened to be successfully found. These results, however, harmonise to some extent with what had been found in the case of plague toxin; and it might be noted that this phenomenon of hyper-sensitiveness was to be found under many other conditions. This harmful action of the toxin would indicate the intra-cellular poisons of the bodies of the micro-

organisms to be probably the most suitable immunising agents, and this view was borne out by the experiments of Foà and Scabia,[1] who state that a watery glycerine extract of the dead bodies of the pneumococci forms a much better immunising medium than the diluted virus itself. Presumably, therefore, this result might be regarded as due to the production in the latter case of the more soluble toxins. The lethal dose of toxin obtainable in these experiments was about one hundredth part of the weight of the animal, which corresponded to the lethal dose of the filtered extract of the blood and tissues of rabbits dead of pneumococcal infection, as was found by Isaeff. The occurrence of fore-leg paralysis in two cases was noteworthy, and, so far as the author knew, hitherto undescribed. It would appear that the poison had a selective affinity for the nerves and their centres supplying these parts. In this research he had had the valuable assistance of Dr. Cartwright Wood, to whose active participation and guidance the work was largely due.

January 16th, 1900.

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12. *The heart of an adult with deformity of the aortic valve, the result, possibly, of intra-uterine endocarditis.*

By F. Parkes Weber, M.D.

Description and remarks.—The heart weighs fourteen ounces and shows some hypertrophy of the left ventricle. I wish especially to direct attention to the condition of the aortic orifice. The contiguous portions of the two anterior valves are so completely united that they may be described as forming a single valve divided into two equal portions by a much "fenestrated" septum or frænum, this frænum representing the portions of two original valves which have become fused together. Just above the frænum, about midway between the orifices of the two coronary arteries, the wall of the aorta is much thickened. The valves themselves are also thickened. There is no sign of recent endocarditis, and I am inclined to think that the valvular disease is

[1] 'Gaz. Med. de Torino,' 92, 13, 14, 16.

of congenital origin, though the patient gave a history of rheumatism.

There are many specimens of fused pulmonary and of fused aortic valves in the London medical museums which I believe support my view. In some specimens two aortic or pulmonary valves are so completely fused together that even the frænum or "crossbar" (*vide* John Hunter's notes) has disappeared. The latter cases can only be of congenital origin. In one such specimen (St. Bartholomew's Hospital Museum, Specimen No. 1319) there are only two valves at the pulmonary, and likewise only two at the aortic orifice. The subsequent thickening of the aortic valves in these cases is doubtless in general largely the result of later disease.

In many instances the original deformity is probably the result of intra-uterine endocarditis, and the later changes are due to recurrence of endocarditis (rheumatic) in extra-uterine life, or to more chronic atheromatous thickening, or to both these causes. Sir James Paget ('Med.-Chir. Transactions,' London, 1844, vol. xxvii, p. 188) was, I believe, the first to draw attention to the frequency with which disease affected the aortic and pulmonary orifices when there were congenitally only two instead of three valves. The "fenestration" of the frænum between the united valves confirms the view that in the present case the valvular deformity is to be regarded as of congenital origin. It is unlikely that after birth the contiguous portions of two valves should unite in such a way that fenestrations in each valve should exactly coincide with each other.

The present specimen is from a man aged 30, who died from enteric fever. During life the heart appeared somewhat enlarged, and there was a distinct diastolic murmur at the base, which, though best heard to the left of the sternum (that is, over the "pulmonary area"), was supposed to be more probably of aortic than of pulmonary origin. The cardiac murmur in association with typhoid symptoms suggested the possibility of infective endocarditis being present, but on the whole it was considered more likely that the patient had enteric fever, and that the cardiac murmur was due to an old valvular lesion. The necropsy has shown this view to be correct.

December 19*th*, 1899.

13. *Shell of a pearl oyster, showing islands of nacre in the hinge ligament, the result, possibly, of traumatic displacement of cells.*

By C. G. Seligmann.

The specimen, which comes from Torres Straits, is one valve of *Meleagrina margaritifera*, known commercially as gold-lipped shell. At the base of the shell along the edge of the hinge ligament, the inner nacreous layer deposited by the mantle is thickened and irregular, while in the ligament itself there are four somewhat oval irregular nacreous islands. On carefully

Fig. 2.

Showing the islands of nacre in the hinge ligament, described in the text. Nat. size.

paring away the ligament these patches were found to extend deeply into the substance of the ligament; one, indeed, came into contact with true shell at its base, while the other islands were

found to be separated from the shell by thin strands of ligament only.

The other valve was not seen, but was stated to present nothing remarkable. The origin of the nacreous patches seems doubtful; perhaps it is an example of defective metaplasia in the epithelium of the shell-gland. Balfour[1] states that "a shell-gland appears at a very early period on the dorsal surface [of the larva] in *Pisidium*, *Cyclas*, and *Ostrea*, and probably in most marine forms. It is somewhat saddle-shaped, and formed of elongated non-ciliated cells bounding a groove. It flattens out, and on its surface is formed the shell, which appears usually to have the form of an impaired saddle-shaped cuticle, on the two sides of which the valves are subsequently formed by a deposit of calcareous salts. In *Pisidium* the two valves are stated by Lankester to be at first quite independent and widely separated, and it has been suggested by Lankester, though not proved, that the ligament of the shell is developed in the median part of the groove of the shell-gland." This view is borne out by Leydig,[2] who describes on the dorsal surface of the shell-gland in *Cyclas* two lateral calcified parts giving rise to the two valves, united by a membranous median portion. If, then, an area of epithelium in the median portion failed to undergo the change which produces the hinge ligament, it might reasonably be expected to produce nacre here, as the epithelium on the outer surface of the mantle does elsewhere. A somewhat analogous condition is met with in the human larynx, where patches of stratified squamous epithelium are scattered about the generally ciliated surface. In this case, however, the ciliated mucosa is embryologically older than the squamous patches. Another view is that the nacreous islands are the result of injury—perhaps caused by the intrusion of some enemy or commensal, or by the heavy boots of a diver who may have ground some of the mantle epithelium into the hinge ligament, while the oyster was too young to be gathered. On this hypothesis the transplanted epithelium would have continued to grow and produce nacre *pari passu* with the growth of the ligament, never being entombed by the latter, and in this respect differing from an implantation cyst in man. It is well known to zoologists that a small crustacean *Pinnotheres* is found

[1] 'Comparative Embryology,' p. 215.

[2] Leydig, quoted by Balfour, *loc. cit.*

in a large percentage of shells opened. Habitually it lives between the oyster's gills, but at times it is found attached to the shell and neatly covered over with a layer of nacre, sure evidence of it having forced its way between the mantle and shell of its symbiote, when it is no longer treated as a guest, but as a foreign body. A small fish, *Fierasfer*, commonly commensal with Holothurians, in the rectal pouches of which it lives, sometimes acts in the same way, and Gunther [1] has figured such a case of *Fierasfer* entombed in nacre. Again, irregular sinuous deposits of nacre are sometimes seen in shells, the calcareous layers of which have been bored by marine worms. The condition described is said by practical pearl fishermen to be rare, and no analogous specimen could be found in the large series of diseased shells in the South Kensington Museum. *February 6th*, 1900.

14. *The cortical changes in acute chorea.*

By Bertram Abrahams.

[With Plate II, figs. 2—4.]

Considering the now general tendency to ascribe to the clinical manifestations of chorea a cortical origin, there is surprisingly little record of the application of modern histological methods to the investigation of that region in the disease. The record of a case in which I had the opportunity of making a *post-mortem* examination may hence prove of some interest. I am much indebted to Dr. J. B. Potter, under whose care the patient was, for permission to use the clinical notes, and to Dr. Mott for his kindness in looking through the specimens, which were prepared in his laboratory at Claybury, with me.

K. C—, aged 28, was admitted to Westminster Hospital on April 30th, 1899, suffering from chorea gravidarum, which had begun in the left side of the mouth five days before. There was nothing significant in the family history, except that the patient's only sister had suffered from chorea when pregnant with her

[1] 'Proc. Zool. Soc.,' 1886.

first child. The patient herself had had scarlet fever when four years old, but no other illness. This was her second pregnancy, the first having terminated in abortion consequent upon a fall. During the present period of gestation she had been much worried, and there was a definite history of a sudden fright.. When admitted the movements implicated the whole of the left side, the right being practically free. During the last ten days of life, however, the right side was on the whole more affected than the left. The urine on admission was highly albuminous, but became much less so later on. There was moderate fever throughout, and at the last mania. She died on June 1st, having been delivered two days before of a child nineteen inches in length. It is probable, therefore, that the symptoms commenced at about the end of the seventh month of pregnancy. There was an apical systolic murmur conducted outwards into the axilla, but no other physical sign of interest was recorded.

At the *post-mortem* examination no naked-eye change was found except hyperæmia of the cerebral cortex and a ring of small firm granulations at the base of the mitral valve. A very careful search failed to detect any trace of embolisms or hæmorrhages. The brain weighed 42 oz., and was found on section to be slightly œdematous, particularly on the right side. Microscopical preparations were stained in various ways, particularly by Nissl's method—alone and with saffranin counter-staining,—and with hæmatoxylin and eosin.[1] The most instructive results are those afforded by a comparison between the right and left parietal lobules.

The left cortex is but little altered; the cells appeared practically normal, but there was a moderate exudation of leucocytes, and a slight increase in the size of the perineuronal lymph-spaces. This obviously corresponds to the short duration and mild character of the right-sided movements. In the right parietal lobule the attention is at once struck by a profuse exudation of small cells, which entirely obliterates all trace of Meynert's columns. By staining with eosin these cells are shown to be uninuclear leucocytes, evidences in other words of fairly prolonged inflammatory change. In some of the sections they can be seen in the act of passing through the walls of the small blood-vessels.

[1] I have to thank my former pupil, Mr. H. Hallilay, for preparing some of the best of the microscopical specimens.

On closer investigation they are found to be located mainly in the perineuronal lymph-spaces, which are generally enlarged throughout; the perivascular spaces are also dilated, and contain many lymphocytes. There is considerable change in the appearance of the pyramidal cells. Many of them are bulged and convex instead of concave laterally; in a large number the processes are indistinct and appear to be broken off. The nuclei are uniformly swollen and pale, but, as is usually the case in allied conditions, the nucleoli stain remarkably well and distinctly. There is, however, a general haziness of the cell protoplasm, the Nissl bodies being ill-marked and in many cases replaced by a diffuse finer granulation; the pigment is also either much diminished in amount or entirely absent. There is no trace either of micro-organisms or of the peculiar granular bodies described by Wollenberg.

The changes here described have mostly been seen and recorded by previous observers; less distinctly, however, in that their papers, with one exception, appeared before the publication of Nissl's method of staining. Thus Charlewood Turner in a study of five cases referred to the swelling of the pyramidal cells, and the faintness with which they could be stained. In one of his figures there is shown, though he does not call attention to the fact, marked dilatation of the perineuronal spaces. In Berkley's case particular mention is made of the increase in size of these spaces, and of the fact that each of them contained from three to five "amœboid corpuscles" (presumably lymphocytes). The granulation of the pyramidal cells is also noted as being finer than normal. Dr. Campbell Thomson, in a communication made to the 1899 Congress of the British Medical Association, stated that he found no changes in the cortex of a case of acute chorea other than swelling of the pyramidal cells. It is very interesting to compare these results, and particularly those of my case, with the important observations of Dr. Mott upon the cortices of patients dying in the *status epilepticus*. The conditions described and figured by Dr. Mott differ in degree only from those seen in acute chorea; in other words, the pathological changes in the cortex in epilepsy are similar to, but more severe than, those in chorea. The obvious inference is that the affection of the brain is in each case really secondary, depending in all probability upon an altered blood-state. Dr. Mott is inclined to ascribe the altera-

tions in the cells in the former instance to modifications in the chemical nature of their lymph environment; those seen in the latter are equally consistent with this view.

It would be manifestly unwise to attempt to construct a theory of the pathology of chorea from a record of the observation of one case. I would venture, however, to submit that it tends to support the following general deductions. Firstly, the changes noted are sufficient to explain the clinical manifestations of the disease on the ground of disturbances in the cells of the so-called motor cortex. Secondly, their nature is such as to be susceptible of complete and rapid recovery, a fact in harmony with the description of the disease as "functional. "Thirdly, there is nothing in them inconsistent with the conception of chorea as an affection produced by a blood-state, namely, the rheumatic toxæmia. I have on a previous occasion endeavoured to show that this idea is supported by observations made from a purely clinical standpoint.

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15. *African Lethargy, or the Sleeping Sickness.*

By Patrick Manson, F.R.S., and F. W. Mott, F.R.S.

(With Plates III—VI.)

Part I.—By Patrick Manson.

Although this disease has been known to Europeans since 1803 (Winterbottom), in consequence of the circumstance that it is confined to a limited area in tropical Africa our knowledge of the clinical characters, ætiology, and pathology is still very incomplete. Owing to the benevolent enterprise of Dr. Grattan Guinness, who within the last few years has been instrumental in bringing three cases of the disease to England for purposes of study, a good deal of light has been thrown on some of these points. Many of its clinical features have been more definitely ascertained; the association of the disease with a peculiar blood-worm has been established; and, thanks to the histological labours of Dr. Mott, here recorded, although the cause and true nature of the disease remain still a mystery, we now know the proximate lesion producing the leading characteristic symptom of sleeping sickness—physical and mental lethargy.

Sleeping sickness has a peculiar geographical distribution. It is apparently confined to the tropical part of West Africa. We have no account of its occurrence as an indigenous affection in the eastern part of the continent, and only a very hazy suggestion that it may occur among the Buck Indians of British Guiana. In West Africa it occurs here and there from Senegambia to S. Paulo de Loanda. The limit of its range in the interior of the continent has not been fixed. Quite recently it has been seen at Timbuctoo on the Niger. It is specially common on the Lower Congo. Dr. Simms and others with local knowledge have informed me that it occurs as far up the latter river as Stanley Falls. In the endemic area it is not equally distributed, but is confined to certain limited districts in which a village here and there is specially victimised. There are large districts in which it does not occur. It is said

that its visitations come and go, many cases occurring in a village for several years in succession, the disease afterwards dying out to appear elsewhere in the neighbourhood.

Although sleeping sickness can be acquired only in particular spots, owing to the great length of the latent period—up to seven years, it is said—the disease may declare itself for the first time when the patient is thousands of miles away from the endemic area. Thus a case not very long ago developed in England in a negro who had been in this country and in good health for three years. During the time of the slave trade the disease was not uncommon in the West Indies among the imported slaves, breaking out several years perhaps after the negro had left Africa. It never became domiciled in the West Indies; there is no record of its occurrence in a negro who had not visited or been born in West Africa.

When it breaks out in a village a considerable proportion of the inhabitants may be attacked; and as it persists for years when introduced, the aggregate mortality may become very large. Parts of the country are, it is said, depopulated by its ravages. Both sexes and all ages are liable; adolescents are said to be the most susceptible. Hitherto there is no well-authenticated record of any European having been attacked.

The symptoms may continue for two or three or even more years before the inevitable and fatal termination. The average duration of the illness is about one year.

Roughly speaking, an ordinary case may be said to exhibit three stages—incipient, declared, and final.

Incipient stage.—This usually commences almost imperceptibly. There is a gradual and perhaps intermittingly deepening languor, muscular and mental. The patient from being bright and cheerful becomes dull and sad, or morose even. There is a corresponding facial expression. He is easily tired, and often falls asleep even while at work. His gait becomes tottery and unsteady, like a man's half asleep, and his muscular strength deteriorates. When asked he may say that he suffers from headache, but he does not, as a rule, complain spontaneously. He is liable to bouts of feverishness, although generally his temperature is subnormal. He is liable also to diarrhœa, or to constipation. Appetite is fair, and for a time nutrition is not seriously impaired.

In *the declared stage* the patient is almost always asleep, or apparently so. He is easily roused, and can be got to answer questions. The answers, though to the point, are brief and come slowly. Memory does not appear to be markedly impaired. He takes food when it is brought to him; but he takes a long time over his meals, and may even fall asleep in the middle of eating. At this stage in many cases a certain amount of muscular tremor may show itself, and not unfrequently there is a tendency to dribbling of the saliva. An exceedingly itchy papular eruption, especially marked on the front of the chest, is almost invariably present. The patient is nearly always scratching some part of his body. At this and even at the earlier stage a general adenitis, often well marked, may also be detected by the swollen, sometimes tender, cervical and other glands. The fundus oculi is healthy. The reflexes, deep and superficial, are normal; the sphincters are not affected; digestion goes on satisfactorily, and nutrition may still not be seriously impaired.

In *the final stage*, from the deepening lethargy and progressing muscular debility the patient is confined to bed; saliva dribbles from the angles of the mouth; bedsores form: muscular spasms of different kinds—local and general—may occur, and are sometimes followed by local pareses. There is now much wasting, and death may take place during an epileptiform seizure, or from some intercurrent disease, such as sepsis from bedsores, diarrhœa, and so forth.

Such is the course in the majority of cases. Not unfrequently the disease is ushered in by a series of epileptiform seizures, or by a maniacal outburst. Either of these may supervene at any time during the progress of the case, to which they may give an epileptic or maniacal character.

A considerable number of *post-mortem* examinations of cases of sleeping sickness have been recorded; there is little uniformity in the accounts of the intra-cranial lesions found. Three examinations have been made in England. In one by Dr. Stephen Mackenzie, and carefully recorded in the twenty-fourth volume of the Clinical Society's 'Transactions,' no coarse lesion was detected either in the brain or cord which could in any way be held to account for the symptoms. Neither in the two cases to which Dr. Mott's paper refers,

beyond slight signs of meningitis in one of them, was any gross naked-eye abnormality remarked. We have no account of the microscopical examination in Mackenzie's case; but in Dr. Mott's examinations a very definite lesion, fully accounting for the symptoms, was discovered. The cause of this microscopical lesion, unfortunately, was not ascertained, or, if discovered, was not connected up with the lesion. The cause, therefore, of sleeping sickness has yet to be demonstrated.

On this subject there have been many conjectures. Poison, malaria, alcoholism, manioc poisoning, nostalgia, venereal excess, and a multitude of other things have been accused. So far, none of these things have been shown to have more than an accidental relationship to the disease.

In Mackenzie's case I found a peculiar bloodworm, which, from its not observing the periodicity characteristic of *F. nocturna*, I called *F. perstans*. In slides of blood subsequently obtained from other cases of sleeping sickness on the Congo I found the same worm, and in the two cases on which Dr. Mott's paper is founded this parasite was also present, in one of them in great abundance. There are, therefore, some grounds for connecting *F. perstans* with sleeping sickness; all the more so seeing that the geographical distribution of the parasite and of the disease correspond in a very curious and suggestive manner. Neither is found in the West Indies, nor in East Africa, nor anywhere else, so far as I know, except in British Guiana among the Buck Indians. I have examined a large number of blood-films from natives of St. Vincent, St. Lucia, and Trinidad, W.I., but though other bloodworms are common enough in these islands, in no instance have I found in a native of any of them *F. perstans*. In British Guiana, on the contrary, although the parasite is absent from the coast regions, it occurs in about half of the Buck Indians of the interior. When this fact was ascertained it became of importance, in trying to establish pathological claims for *F. perstans*, to ascertain if these Demerara Indians are subject to sleeping sickness. Dr. Ozzard informed me that during one of his visits to this people a woman was brought to him for treatment on account of her incessant somnolence. Further, a clergyman who had worked much among the Bucks told me that in certain cases of illness these savages take to their hammocks for months before death,

suffering apparently from some affection in which somnolence is a marked symptom. Can this be sleeping sickness? It would be unwise to attach too much importance to these statements; the subject requires further investigations. But should it be found that the Buck Indians of Demerara are liable to sleeping sickness, the case in favour of *F. perstans* will be very much strengthened, seeing that theirs is the only country outside West Africa in which *F. perstans* is found.

Unfortunately for the claims of this parasite, there is one circumstance which must be held to tell very much against it. In my inquiries into the distribution of *F. perstans* on the Congo and in other parts of West Africa I found that in many places quite 50 per cent. of the population harboured this worm, and that both in places in which sleeping sickness was common, and in places where apparently it is unknown. It is evident from this that if *F. perstans* be responsible for sleeping sickness some additional factor must come into operation. So far there is no insuperable obstacle to the acceptance of the hypothesis, for in helminthology there are many instances of parasites which are only occasionally pathogenic—*F. nocturna*, for example.

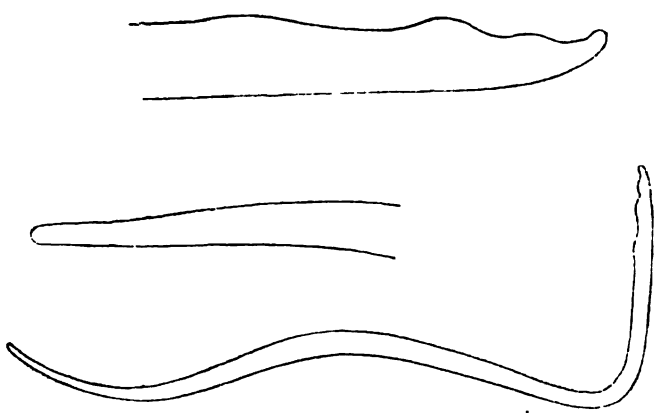
Such an hypothesis would explain the latency which, in many instances, is so remarkable a feature of the disease. It would also explain its uncommunicability unless within particular geographical areas; for, like all similar parasites, *F. perstans* must pass through an intermediary host before it can enter its definitive host, and this intermediary host is most probably an animal with a circumscribed geographical range. The disease, therefore, can be acquired only within this circumscribed area.

At one time I supposed the peculiar itching papular eruption, so common on the skins of sleeping sickness patients, might be produced by the embryo *F. perstans* seeking its way out of the body, as happens in certain similar parasites of the lower animals, and that the filariform embryo which Dr. John O'Neil found in what he calls craw-craw in natives of West Africa was this parasite so engaged. I examined the papules in both of our cases with this point in view, but, although I found plenty of *F. perstans* in the papules when the scratching and pricking at the examination drew blood, I did not once discover

any advanced developmental form, or anything to lead me to believe that this conjecture was well founded. I have little doubt that the filariform parasite observed by O'Neil in craw-craw was either *F. perstans* or some other bloodworm which had become distorted by endosmosis of the water in which O'Neil teased up the tissues he examined; the parasite he found was, in fact, one which had escaped in the blood when the papule was cut into.

In the younger of our patients the filariæ in the blood diminished very much in their numbers before his death; doubt-

FIG. 3.



A diagram of the immature Filaria referred to on p. 105, as found in the lung; the lowest figure represents the entire worm; the middle and upper represent still more enlarged outlines of the head and tail respectively

less the parental worms suffered in consequence of the extreme degree of innutrition of their host. In this patient no parental forms were discovered. But in the elder patient, he who died suddenly of hyperpyrexia, several parental forms were discovered—one in the connective tissue behind the abdominal aorta, and five or six in the mesentery. These worms were mostly in fragments, broken up by the needles in teasing up the tissues in the search for them. I cannot say if they lay in lymphatic, in blood-vessel, or in connective tissue. They measured from 70 to 80 mm. in length by 0·120 mm. in breadth, were smooth on the surface, cylindrical, had rounded cephalic

extremity with a simple unarmed mouth, and a peculiar and characteristic tail furnished with two triangular chitinous appendages. The characters of the male worm could not be made out, as no unmutilated specimen was obtained. Sufficient evidence was discovered, however, to enable us to pronounce that this West African worm is identical with the parental form found some time previously by Daniels in Buck Indians of Demerara ('Brit. Med. Journ.,' April 16th, 1898; June 17th, 1899).

In a minute suppurating cyst in the apex of the left lung of this patient I found an immature worm about 1·22 mm. in length; I have little doubt it was an immature *Filaria perstans*. Its position in the lung shows that the parasite may invade a variety of organs.

Assuming that *F. perstans* is the cause of sleeping sickness, its *modus operandi* would form an interesting subject for investigation by future observers.

The changes in the central nervous system of two cases of African lethargy.

PART II.—BY FREDERICK W. MOTT, F.R.S.

Two of the three cases of Congo sickness referred to by Dr. Manson in the preceding portion of this communication, were admitted into Dr. Abercrombie's wards at Charing Cross Hospital last year, and for a short time were under my care; a lecture with an account of these two cases, by Dr. Manson, was reported in the 'British Medical Journal.'* These patients subsequently died, and the central nervous systems were handed to me for investigation. Before proceeding to describe the changes which were found, and which are illustrated in the accompanying plate, it will be well to describe the principal clinical phenomena presented by the patients; this I am enabled to do by making a summary from the case-book notes carefully abstracted by the house physician, Mr. Clogg, to whom I wish to express my obligations.

* Dec. 3rd, 1898, p. 1672.

Case 1.—Eli Mboko, aged 20, was a Congolese school teacher of exceptional talent, speaking English perfectly, and having translated a book from English into his native language. His illness commenced twelve months before admission to the hospital on September 24th, 1898. Previously cheerful, interested in his avocation, he became vacant-minded and miserable, with little interest in his daily work, and as the disease progressed he would frequently fall asleep while at his work. These symptoms became more pronounced as time went on, but during his voyage to England he appears to have improved a little. Upon admission to the hospital, he was found to be fairly well nourished. The skin had to some extent lost its natural glossy condition, and there were a few papules over the abdomen. There was a general enlargement of the lymphatic glands, but they were discrete, and not anywhere massed together.

Nothing abnormal was found in the thorax or abdomen. Parchment scars on the front of both legs were evident. Examination of the eyes by Mr. Treacher Collins revealed nothing abnormal.

Examination of the fæces showed presence of the ova of the following parasites: *Ankylostoma duodenale, Trichocephalus dispar, Ascaris lumbricoides* (these parasites were treated successfully by anthelmintics). Examination of the blood by Dr. Manson on numerous occasions showed nothing markedly abnormal except the presence of the embryo *Filaria perstans* although there was some slight degree of anæmia.

The striking features to be associated with the nervous lesions, and which continued and progressed till the fatal termination, were:

1. Lethargy and a tendency to sleep the greater part of the day. From this drowsy condition the patient could always be aroused.

2. Slowness of speech without any tremor and without any noticeable change, except that there was an unwillingness to respond to questions, owing to a sense of fatigue and drowsiness. The reaction time, as denoted by the time taken to frame an answer in response to a question, was much prolonged. When the patient spoke he usually made a curious grimace—elevation of the upper lip and nostrils.

3. Progressive motor enfeeblement, paresis like a man who had suffered a long illness. His gait also was that of weakness rather than paralysis or ataxy. He shuffled along, hardly lifting his legs from the ground, and with a wide base. Occasionally he would reel; there was nothing noteworthy about the reflexes, but the muscles, as indeed the whole body, were wasted, although the appetite was fairly good. There was no loss of sensation, and he complained of no definite pain except a pain in the back of the head, which he had had early in the illness. He suffered for some weeks with gingivitis.

4. The temperature until just towards the end of life, when hyperpyrexia occurred, was either normal, subnormal, or very slightly raised, and the pulse denoted low arterial pressure.

The condition of the patient did not show any very marked change until about three weeks before he died, when he was noticed to breathe very deeply, and the alæ nasi could be seen working. Examination of the chest revealed nothing, but his breath was very fœtid. He had no cough; respirations were never more than 28. Two days before death a marked dyspnœa occurred. Respirations now became 48 to 56, and were very irregular. Only a little bronchitis and hypostatic congestion could be ascertained by physical examination, and his temperature rapidly rose on February 11th and continued until the night of February 13th, when in the axilla the thermometer recorded 108·6°, and he died. His weight on admission was 7 st. 3 lbs., at death 5 st. 7 lbs. The fœtid breath which occurred some weeks before his death could be accounted for by a fœtid expectoration which he coughed up. It was turbid, blood-stained, and very foul; it no doubt came from an abscess which was found *post mortem* in the lung. Whether it was the cause of the hyperpyrexia or not it is difficult to say. Muscular tremors were observed only during the last hours of life, and there were never any fits or twitchings or periods of maniacal excitement during the course of this patient's illness.

Necropsy.—The following is an extract of the notes of the necropsy made by Dr. William Hunter. Body very emaciated; no rigor mortis. All the organs, with the exception of those mentioned especially, may be considered as having presented

normal appearances, although wasted. In the upper lobe of the left lung there was a small nodule half an inch in diameter, which on section proved to be a small abscess cavity containing thick pus, which on microscopical examination was found to contain an immature disorganised parent worm. Close to this were two smaller abscesses. The pus-containing cavities were close to a branch of the pulmonary artery, but there was no connection, nor did there appear to be any connection between these abscess cavities and the bronchi. The lungs otherwise appeared healthy. No *ankylostoma* found in the duodenum. An adult *Filaria* was found by Mr. O'Neil in the retro-peritoneal tissue near the aorta, and also several others at the root of the mesentery. These were subsequently identified by Dr. Manson as identical with those described by Dr. Daniels as occurring in the Buck Indians of British Guiana. The heart was very small, weighed only 5½ ozs., and the muscle had a pale hyaline appearance. Central nervous system: Removal of the skull-cap; the calvarium dense and hard, rather thin, symmetrical. Dura mater not adherent, longitudinal sinus empty. No marked excess of cerebro-spinal fluid, ventricles neither dilated nor granular. Slight pia-arachnoid thickening; right hemisphere, weight 1 lb. 6 ozs.; left, 1 lb. 6 ozs.; cerebellum, 6 ozs. Convolutions not wasted, complex, and to all appearances a very well-formed brain. The spinal cord and spinal ganglia showed nothing abnormal to the naked eye. They were preserved in 5 per cent. formalin, and subsequently the portions were hardened in various fluids for microscopical examination.

The change which I believe essential to this disease was found in both cases, and will be described with the next case.

Case 2.—Tenda Mkaloo, aged 11, admitted September 24th, 1898. This patient was unable to speak English, and his fellow sufferer conversed with him and for him. Supposed date of illness three or four months prior to admission. He was carried into the hospital partly on account of his weakness, partly on account of his drowsy condition. Weight 3 st. 11 lbs. Very emaciated, and there was a certain amount of proptosis, for the eyelids did not meet during sleep, the sclerotics being visible. Skin dry and lustreless, covered on the thorax and abdomen with numerous papules. Marked pruri-

tus, slight conjunctivitis and excessive lachrymal secretion. Marked dribbling of saliva, fœtid breath, tongue furred but moist; lips dry and covered with dry epithelium. Hair was not tinged red; he was evidently full of fear, and whether this was the cause of his disinclination to palpation or whether it was actual pain could not be discovered. There was general glandular enlargement, as in the other case, only more marked. He constantly put his hand to his neck, which appeared to pain him; the cervical glands were much enlarged. Thorax, heart, and lungs normal; abdomen uniformly enlarged and flaccid; spleen, extended to the level of the umbilicus, was hard and smooth, and the edge sharp, not tender. Edge of liver could be felt three fingers' breadths below the costal margin, sharp; surface of the liver smooth, not tender. Fæces contained the same parasites as Case 1. Eyes, examined by Mr. Treacher Collins, found to be normal.

The patient presented the same characteristic features as regards mental and motor enfeeblement (but more marked), combined with lethargy, and a mournful expression, as Case 1, except that the knee-jerks were slightly exaggerated and plantar reflexes brisk; moreover, towards the end of life epileptiform convulsions, contracture of the limbs, retraction of the head and neck, unconsciousness, and Cheyne-Stokes breathing developed, but no hyperpyrexia.

Examination of the blood by Dr. Manson showed the presence of the embryo *Filaria perstans*, but nothing else noteworthy is recorded. The intestinal parasites were cleared out with thymol, and his general condition and weight improved. Decrease in size of the liver, spleen, and lymphatic glands took place. Six weeks after admission some cervical glands were removed by Mr. Boyd, and 5 c.cm. of blood was withdrawn from the median basilic vein in the arm by means of an aseptic syringe. No benefit resulted from operation.

Dr. Bulloch placed $2\frac{1}{2}$ c.cm. into each of two tubes of bouillon. He also attempted to make cultures from the gland on glycerine agar. None of the cultures had grown at the end of three weeks; he therefore came to the conclusion that no ordinary micro-organisms were contained in the blood or glands. Neither could I by staining sections show tubercle bacilli in the glands. I regret, however, that lumbar punc-

ture was not performed and cultures taken from the cerebro-spinal fluid.

On February 4th a fine tremor of the right hand developed, and a few days later a tremor of left arm and hand. The gums became spongy, and there was a foul-smelling discharge from the mouth. A little later retraction of the head and neck occurred, and he began to pass his urine under him. On February 14th contracture of the thighs on the abdomen and of the legs on the thighs was noted, and he was frequently found crying and moaning as if in great pain. The knee-jerks were active, and there was no ankle clonus. His appetite failed, and he could only take fluid nourishment.

On February 21st the first fit occurred, and was succeeded in twelve hours by seventy-five others. They started with conjugate deviation of head and eyes to the right, the right side of the face was drawn, the jaws were at first clenched; the eyelids opened and closed very quickly, and the eyeballs were jerked from side to side. The arm was next flexed at the elbow and wrist, and the fingers flexed into the palm. The right leg then became rigid.

After the clonic spasm there was relaxation of the right side, and the left side passed through a tonic and clonic stage. At first the convulsions lasted for from 2½ to 3 minutes, and they followed one another in rapid succession. Later there was a greater interval between the fits, and they were of shorter duration, and did not extend to the left side of the body. The breathing in the interval between the fits (when there was any interval) was at first quite regular and shallow, about 24 per minute. During the two following days the patient had twenty-three more fits, making altogether ninety-eight in three days. The temperature during the fits was 103° on an average. The breathing became irregular, and was at one time typical Cheyne-Stokes. The patient was completely unconscious during the fits, also during the intervals, which were short; but when later a longer interval took place he became semi-conscious. Occasional irregular spasms followed twitching of the face muscles, especially of the left side, and risus sardonicus, with a peculiar catching breathing as if there were spasm of the diaphragm. Bedsores began to appear on the trochanters and sacrum. On March 12th patient appeared

to be in great pain, crying out frequently, so that he had to be placed in a special ward. He had to be fed by the nasal tube. On March 19th patient had ninety-four more fits, similar to those previously described. He continued to have epileptiform fits, and later there appeared to be paresis of the right facial muscles and arm, as he was never seen to move the latter, although he did his left arm. On March 19th the temperature became subnormal, never rising above 96° until his death on April 2nd. During the last few days of his life he had several fits a day, and the rigidity seemed to pass off in a measure. He was quite unconscious at the end, and appeared to have paralysis of the muscles of deglutition.

Necropsy.—The following is the report of a *post-mortem* examination made by Dr. William Hunter: Body extremely emaciated, weight 3 stone. Bedsores on all prominences. Relations of organs in the thorax and abdomen natural. Mesenteric glands enlarged. No pleural or peritoneal effusions. Bronchial glands enlarged. Right lung: lower lobe exhibits a consolidated patch with recent lymph on pleural surface; on section this appears like a tuberculous mass with circumscribed pneumonia. Discrete nodules, shot-like to feel, exist throughout the lungs. No cysts or abscesses. Heart small, muscle shows pigmentation. Kidneys small, each 2½ ounces, natural appearance. Thyroid, spleen, stomach normal, also intestines, with exception of duodenum, which shows a few patches of congestion here and there. Liver apparently normal in appearance. Bladder normal.

The brain was taken out soon after death. The dura mater was adherent to the calvarium. The cerebro-spinal fluid was slightly turbid, but colourless and in excess. The pia-arachnoid over the convexities was thickened and opaque, but could be stripped without erosions; no marked flattening of convolutions, nor wasting. The ventricles were not dilated and the ependyma was not granular. The spinal cord and ganglia were removed, and appeared healthy except at the lower part, where there was inflammation of the meninges due to extension from the large and very deep sacral bedsore. No doubt the gelatinous yellow deposit around the roots of the cauda equina was due to extension of septic inflammation

from the bedsore. The cerebro-spinal fluid was examined for micro-organisms by cultures, etc., and various organisms including diplococci, streptococci pyogenes, and bacilli were found, but, of course, under the circumstances no importance could be attached to these observations. Embryo *Filariæ* were found alive in this fluid (which, however, contained a little blood) thirty-six hours after removal from the body. Both in this case and in Case 1 the pituitary body was in all respects normal. In both cases after hardening in 5 per cent. formalin the central nervous system and especially the medulla showed marked puncta cruenta. The vessels of the brain in neither showed any naked-eye abnormality. Portions of the brain, basal ganglia, pons, medulla, spinal cord, cerebellum, and spinal ganglia were hardened respectively in alcohol, Müller's fluid, Marchi's fluid, and 5 per cent. formol, and after fixation were embedded in celloidin or paraffin; thin sections were cut and stained by Nissl, Marchi, and Marchi-Pal methods. The microscopical appearances in both cases exhibited essentially similar but not identical conditions. There were in both instances lepto-meningitis and encephalo-myelitis. Throughout the whole central nervous system, but especially in the medulla and at the base of the brain, sections showed the pia-arachnoid infiltrated with mononuclear leucocytes; the inflammation could be traced along the blood-vessels and septa into the substance of the nervous system (*vide* Plate IV, figs. 1, 2; Plate VI, fig. 3).

The peri-vascular lymphatics around both large and small vessels were crowded with these lymphocytes. The left cerebral hemisphere of Case 2 showed a more intense inflammation than the right, and the infiltration of the membranes was more marked, which very probably may be associated with the right-sided fits, especially as one found in the motor region of this side more disorganisation of cells (*vide* Plate IV, fig. 3).

Sections were stained by Gram, Pfeiffer, and many other methods for micro-organisms, but with negative results. Considering the universal evidence of intense chronic inflammation, the wonder is that the ganglion cells did not present more marked evidence of disorganisation. By Nissl method the cells of the cerebral cortex in the motor region of Case 1

showed a normal outline, but scattered through the substance, especially in the pericellular spaces, are the small round nucleated cells (*vide* Plate IV, fig. 2). In all other parts of the nervous system of Case 1 the outline of the cells is fairly normal, but owing to the hyperpyrexia characteristic bio-chemical change had taken place in all the nerve-cells. The Nissl bodies were neither visible in the cells nor upon the processes, the whole neuron being uniformly stained by the dye instead of showing the normal differentiation into achromatic and chromatic substances. The columns of Meynert were preserved, and if there had been no hyperpyrexia I doubt if much change would have been visible in the neurons.

In Case 2 the cortex cerebri, especially of the left side, showed more marked cellular, but not very much more marked peri-vascular, changes. The columns of Meynert were disorganised, the outline of a great many of the pyramidal cells, large as well as small, altered and irregular, indicating disorganisation and destruction (*vide* Plate IV, fig. 3, and compare with Plate IV, fig. 2, from Case 1). In the spinal cord and various other parts of the central nervous system numbers of cells of fairly normal appearance existed, and in these the Nissl bodies appeared natural (*vide* Plate V, fig. 4). The medulla showed to the naked eye marked congestion of the vessels; and, microscopically examined, the evidence of chronic inflammatory reaction around the vessels and in the membranes was profound. Very many of the nerve cells were shrunken and atrophied, others showed chromatolysis, and not many normal cells were discoverable.

Fibres.—Sections of the brain and spinal cord were stained by Marchi, Marchi-Pal, and Carmine-Weigert* methods. Nothing abnormal was found in Case 1, with perhaps the exception that the tangential and supra-radial fibres were not quite so numerous as normal. In Case 2 there was obvious atrophy of both these sets of fibres, and also to a less degree of the inter-radial fibres in the motor regions of both hemispheres, but especially the left (*vide* Plate VI, figs. 1, 2).

Examination of the spinal cord showed no degeneration or sclerosis in Case 1, whereas in Case 2 there was a slight diffuse sclerosis (*vide* Plate V, fig. 2) in the pyramidal tracts, especially

* See Addendum, p. 117.

of the right side, with recent degenerated fibres. There was no degeneration in the anterior or posterior roots. The arteries showed no endarteritis in either case, but in the choroid plexus there were numerous psammomata, caused, I believed, by degenerated and occluded vessels. The epithelium appeared quite normal. The spinal ganglia showed the same evidence of a chronic inflammatory process; but with the exception of the hyperpyrexial change of Case 1, the cells appeared otherwise fairly normal. The central canal of the spinal cord was filled up with proliferated glia tissue in both cases.

Remarks.

The condition common to both cases was a meningo-encephalo-myelitis. MM. Regis and Gaide* have attributed the symptoms to a diffuse meningo-encephalitis of infective origin. They described, however, the clinical symptoms only of a case observed in the region of Timbuctoo; but, so far as I know, this is the first detailed microscopical examination which has been made.

With the exception of the lymphatic glands, liver, and duodenum, the examination of the other viscera revealed nothing noteworthy. Sections of the lymphatic glands showed a proliferation of lymphocytes; sections of the duodenum showed also a large number of lymphocytes, and increase in size of the lymphoid nodules; sections of the liver showed a little chronic interstitial inflammatory change, scattered and variable in degree, and probably to be associated with the duodenal parasites.

Both the clinical history and the morbid appearances point to a chronic process. I will not speculate upon the pathogeny of the disease, although I cannot refrain from expressing the opinion that it is due to a poison, of micro-parasitic or other source, which affects especially the lymphatic system, and in particular that portion of it pertaining to the central nervous system. The lethargy, together with progressive motor and mental enfeeblement, could be explained either by the action of a toxic agent, circulating in the cerebro-spinal fluid upon the vital activities of the neurons, or simply by the accumula-

* 'Presse Médicale,' Oct. 1st, 1898.

tion of lymphocytes around all the blood-vessels interfering with the metabolic exchanges between the blood and the nervous elements. Although the existence in such abundance of mononuclear leucocytes would rather indicate the existence and prolonged action of a noxious agent which would be capable of damaging the nervous elements. The mechanical theory, however, has some support, seeing that a somewhat similar condition of drowsy stupor, progressive paresis, and dementia, with epileptiform convulsions, may be brought about by internal hydrocephalus occasioned by tumour of the third ventricle.* Whether the hyperpyrexia in Case 1 can be attributed solely to the encephalo-myelitis I cannot say, seeing that there was a fœtid abscess in the lung, but I think it is probable. The right-sided fits, the muscular tremors, and the contracture in Case 2 were undoubtedly due to the inflammatory changes, with irritation and destruction of the nervous elements in the cerebral cortex, especially of the left hemisphere.

Another question might be asked: Is this a nervous manifestation of constitutional syphilis, akin to general paralysis, which also by some authorities is considered to be a primary meningo-encephalitis. The geographical and epidemiological character of the disease, together with the absence of granular ventricles and the universal inflammatory condition, is against this hypothesis, although sections of the motor cortex of Case 2 might upon microscopical examination pass for general paralysis; but I have never in the most acute forms of general paralysis seen so much and so general an inflammatory condition of the vessels; yet the nerve-cell changes of this disease, which may last years, are slight in comparison with that other almost invariably fatal disease, general paralysis. This offers to my mind a strong argument in favour of the theory that general paralysis is a primary degeneration of the neuron with secondary inflammatory changes.

Neither Dr. Bulloch's observations nor my own support the

* Likewise in a case of leukæmia, which I have recently had the opportunity of examining, the patient suffered with motor paresis and attacks of drowsy stupor terminating in coma and death; the brain showed no naked-eye change, but sections examined microscopically exhibited a most striking appearance, owing to the distension of the capillaries and veins with myelocytes and leucocytes. There was, however, very little organic change in the nerve-cells.

observations and experiments of MM. Gagigal and Lepierre, published in the 'Comptes Rendus de la Société de Biologie,' January, 1898, in which they claim to have isolated a bacillus from the blood which grows upon serum, upon gelatine, and in bouillon. These authors claim to have produced the disease in animals, but MM. Brault and Lapin obtained some of the cultures, and were unable to confirm the results ("sur l'Etiologie et la Pathogénie de la Maladie du Sommeil," 'Archives de Parasitologie,' etc., July, 1898). Again, M. Marchand ("Rôle du Pneumocoque dans la Pathologie de la Maladie du Sommeil," 'Annales de l'Institut Pasteur,' March, 1899) attributes the disease to the pneumococcus rather by inference than proof. Still, I regret that Quincke's lumbar puncture was not performed and the cerebro-spinal fluid tested as I suggested.

The negative evidence obtained by Dr. Bulloch and myself as regards micro-organisms does not preclude the possibility that the disease is due to a living organism, for no organism has been discovered in rabies, nor has a specific organism been found for syphilis.

Valuable confirmation of these observations has been afforded me by the kindness of Dr. Stephen Mackenzie. Having read the very interesting clinical report of a case under his care in 1890, published in vol. xxiv of the Clinical Society's 'Transactions,' I inquired of him whether any microscopical examination of the central nervous system had been made. He kindly sent me a set of specimens, comprising sections of most of the organs, of the occipital, temporo-sphenoidal lobes, and of the corpus striatum. The specimens were stained with carmine and logwood and eosin; they show the same evidence of chronic meningo-encephalitis that I have detailed in the above cases. All the peri-vascular spaces are crowded with mononuclear leucocytes; but the method of hardening and staining employed does not lend itself to a study of the condition of the nerve-cells. A fuller account of this case and of the histological changes in the organs will be found in the succeeding communication. Judging from these results, it is highly probable that meningo-encephalitis is the constant anatomical lesion of negro or African lethargy.

In conclusion I wish to express my indebtedness to Dr.

DESCRIPTION OF PLATE III,

Illustrating the communication on African Lethargy by Patrick Manson, F.R.S., and F. W. Mott, F.R.S. (Page 99.)

FIG. 1.—An entire female of *Filaria perstans*.

FIG. 2.—The head of female.

FIG. 3.—The tail of female.

The three preceding figures are from microphotographs by Mr. Francis Fowke, taken from specimens furnished by Mr. C. W. Daniels, and described in the 'British Medical Journal,' June 17th, 1899. The parasites were found in aboriginals of British Guiana. The use of the blocks has been kindly allowed by the proprietors of the 'Journal of Tropical Medicine.'

FIG. 4.—Section of central canal, lumbar spinal cord, Case 1. The canal is filled with proliferated glia tissue, and there is a marked increase of the lining epithelial cells. Magnification 90.

FIG. 5.—Section of the pia-arachnoid septum of the anterior median fissure of the spinal cord, Case 1. A small artery is seen cut transversely, surrounded by mononuclear leucocytes. Magnification 400.

FIG. 6.—Transverse section of a small vein in the medulla, in the neighbourhood of the hypoglossal nucleus the cells of which showed marked degenerative changes. It will be observed that the perivascular lymphatic sheath is crammed full of leucocytes. Magnification 250.

From microphotographs.

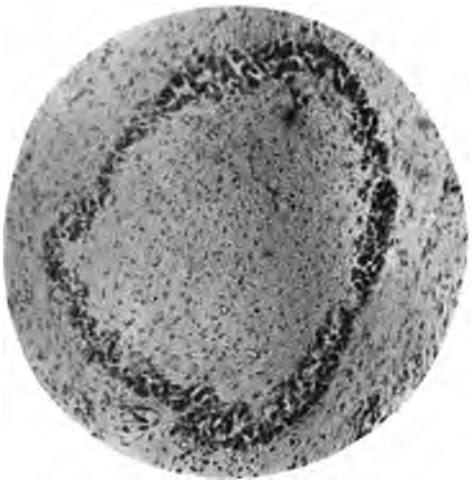


Fig. 4.

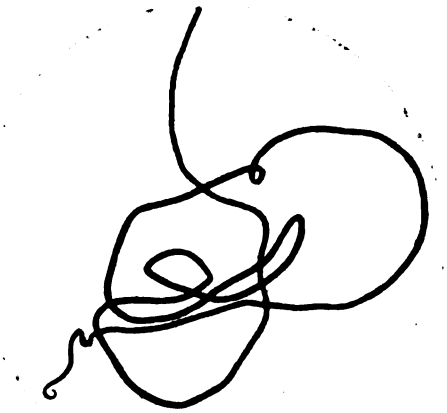


Fig. 1.

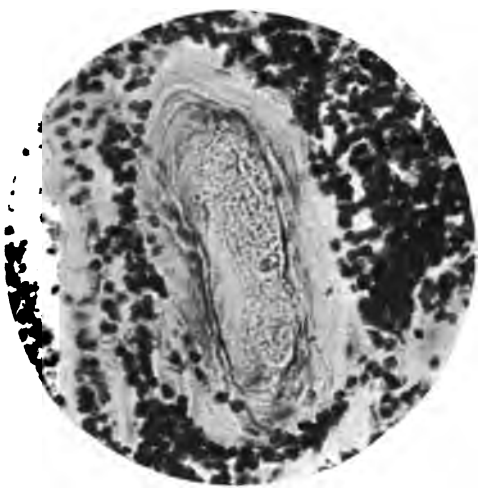


Fig. 5.

Fig. 2.

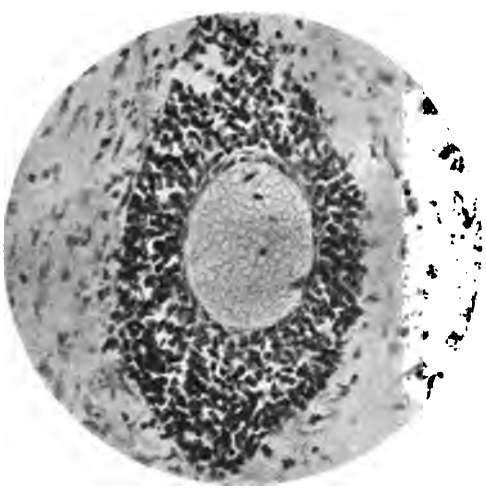


Fig. 6.

Fig. 3.

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DESCRIPTION OF PLATE IV,

Illustrating the communication on African Lethargy by Patrick Manson, F.R.S., and F. W. Mott, F.R.S. (Page 99.)

FIG. 1.—Section of medulla in the neighbourhood of the hypoglossal nucleus, stained by Nissl method, showing a small vessel with perivascular lymphatic space distended and filled with deeply stained mononuclear leucocytes. In the neighbourhood are two ganglion cells showing early degenerative changes. Magnification 250.

FIG. 2.—Case 1. Section of cerebral cortex. The pyramidal cells have a normal appearance in outline, but are uniformly stained owing to the hyperpyrexia. A large number of small deeply stained cells, mostly leucocytes, are seen in the pericellular spaces and around a small capillary vessel. Magnification 250.

FIG. 3.—Case 2. Section of motor cortex. The cells are diffusely stained, irregular in outline, their processes broken off, and the arrangement of Meynert's columns displaced. There is glia-cell proliferation and some leucocytic infiltration. The outline of the cells contrasts markedly with fig. 2. The microscopical appearances closely correspond with those observed in general paralysis. Magnification 250.

The chromolithographs are drawn from microphotographs.

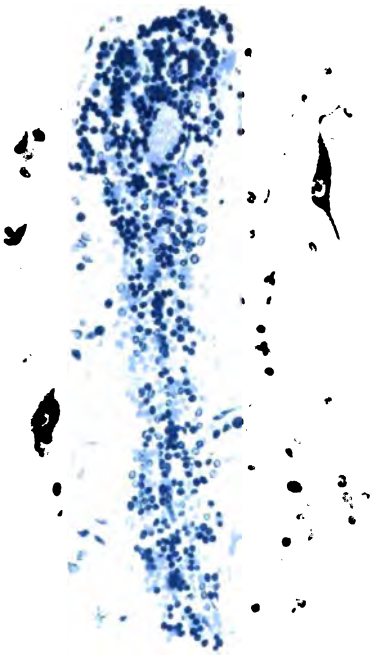

Fig. 1.

Fig. 2.

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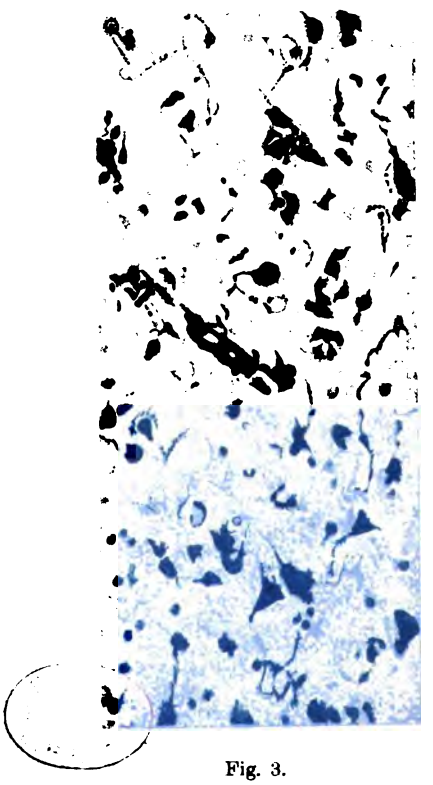

Fig. 3.

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DESCRIPTION OF PLATE V,

Illustrating the communication on African Lethargy by Patrick Manson, F.R.S., and F. W Mott, F.R.S. (Page 99.)

FIG. 1.—Case 2. Transverse section of the spinal cord. Magnification 10 diameters.

FIG. 2.—Case 2. Transverse section of a small portion of the crossed pyramidal tract, showing a slight diffuse sclerosis with scattered recently degenerated fibres. Magnification 300.

FIG. 3.—Case 1. Section of anterior horn, lumbo-sacral enlargement, showing anterior horn cells slightly swollen, uniformly stained, granules of Nissl no longer visible on the dendrons, nucleus swollen, clear and distinct. Some leucocytic infiltration of surrounding tissue. Magnification 300.

FIG. 4.—Case 2. Section of anterior horn, lumbo-sacral enlargement. The anterior horn cells show a fairly normal appearance, the Nissl granules are seen distinctly on the processes and in the bodies of the cells. In this case there was no hyperpyrexia, which was undoubtedly the cause of the change of appearance in fig. 3. The surrounding tissue, however, shows a much more marked leucocytic infiltration. Magnification 300.

The chromolithographs are drawn from microphotographs.

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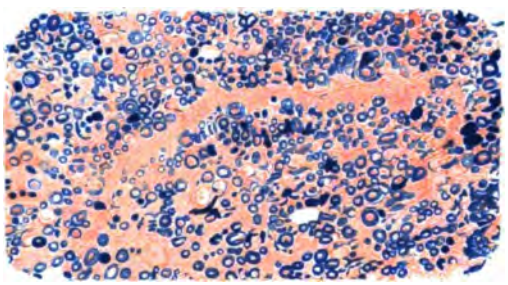

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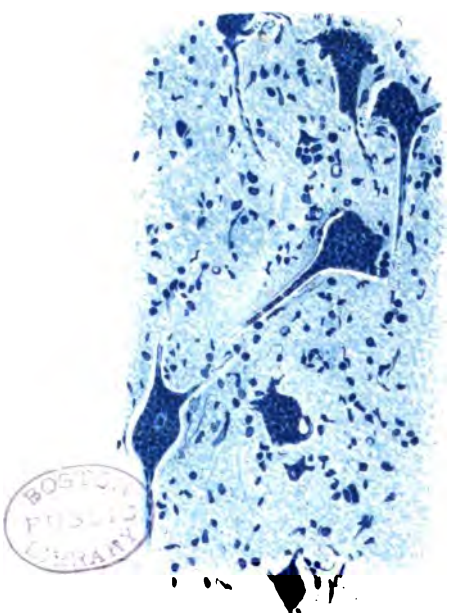

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DESCRIPTION OF PLATE V,

Illustrating the communication on African Lethargy by Patrick Manson, F.R.S., and F. W Mott, F.R.S. (Page 99.)

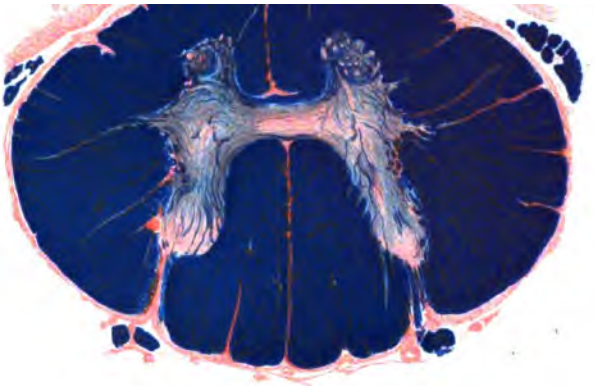
FIG. 1.—**Case 2. Transverse section of the spinal cord. Magnification 10 diameters.**

FIG. 2.—**Case 2. Transverse section of a small portion of the crossed pyramidal tract, showing a slight diffuse sclerosis with scattered recently degenerated fibres. Magnification 300.**

FIG. 3.—**Case 1. Section of anterior horn, lumbo-sacral enlargement, showing anterior horn cells slightly swollen, uniformly stained, granules of Nissl no longer visible on the dendrons, nucleus swollen, clear and distinct. Some leucocytic infiltration of surrounding tissue. Magnification 300.**

FIG. 4.—**Case 2. Section of anterior horn, lumbo-sacral enlargement. The anterior horn cells show a fairly normal appearance, the Nissl granules are seen distinctly on the processes and in the bodies of the cells. In this case there was no hyperpyrexia, which was undoubtedly the cause of the change of appearance in fig. 3. The surrounding tissue, however, shows a much more marked leucocytic infiltration. Magnification 300.**

The chromolithographs are drawn from microphotographs.



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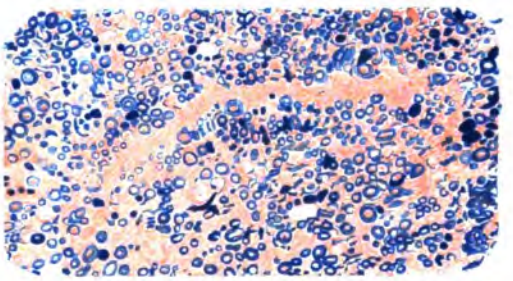

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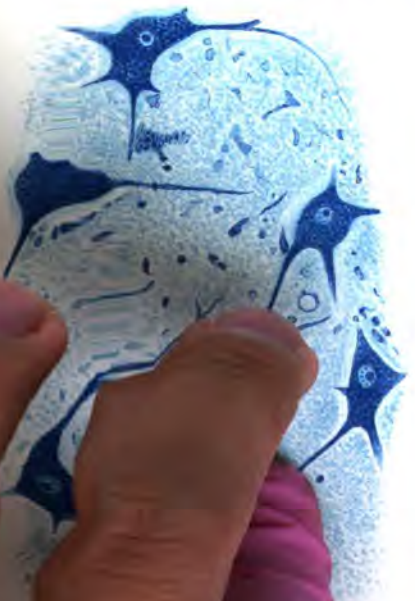

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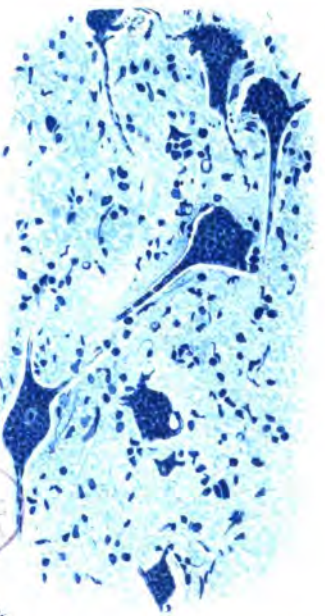

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DESCRIPTION OF PLATE VI,

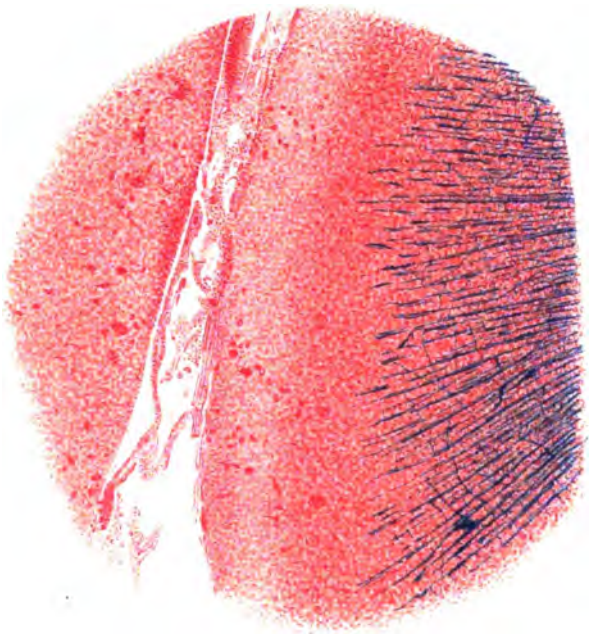
Illustrating the communication on African Lethargy by Patrick Manson, F.R.S., and F. W. Mott, F.R.S. (Page 99.)

FIG. 1.—Case 2. Section of leg area motor cortex, stained by Carmine-Weigert method, showing absence of tangential fibres in the adjacent ascending frontal and parietal convolutions. There is also a marked diminution of the inter-radial association fibres. Magnification 40.

FIG. 2.—Section of the same portion of the cortex in a region where there are a few atrophied tangential fibres still left. On the surface is seen the pia-arachnoid infiltration with leucocytes. Magnification 300.

FIG. 3.—Case 1. Section of leg area of motor cortex, showing a wealth of tangential fibres, and pia-arachnoid infiltration by leucocytes. Magnification 300.

The chromolithographs are drawn from microphotographs.



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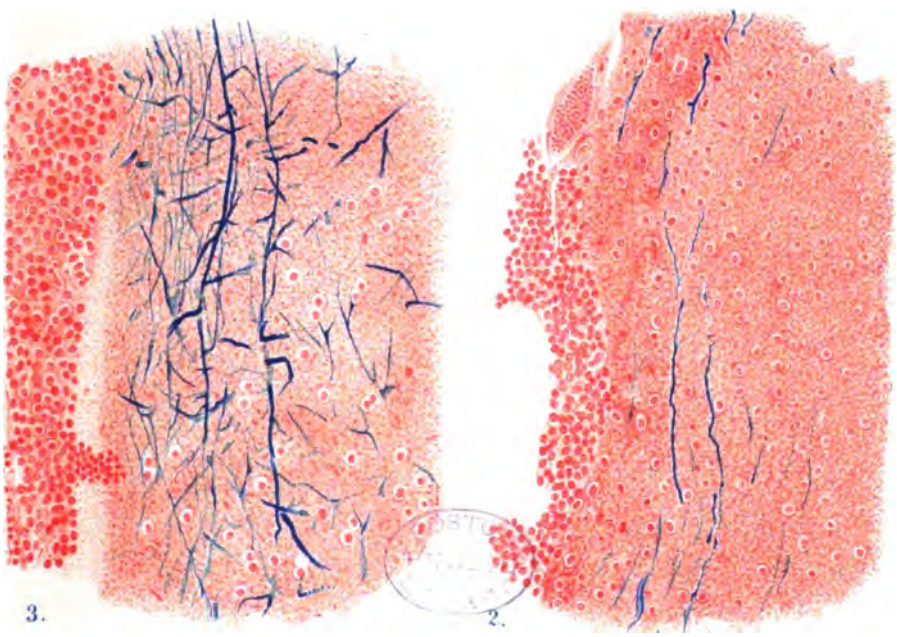

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Manson and Dr. Grattan Guinness for giving me the opportunity of making the above investigations.

Addendum.

The Carmine-Weigert staining method, which I have adopted for staining sections of the central nervous system, is a combination of the von Gudden and Weigert methods. It combines the advantages of both, and as I have not hitherto described it, it may be worth while to do so here. Portions of the tissue which have been hardened in Müller's solution, or in equal parts Müller and 5 per cent. formalin, are washed in running water, till no more colour comes out. They are then placed in a solution of 2 per cent. carminate of soda, and kept in a warm chamber for three or four days. The tissue thus stained in bulk is rinsed with water, and subsequently embedded by the usual method in celloidin. Sections are then cut and stained by the Weigert method. The cells are stained an orange red, as is likewise the neuroglia; the fibres are stained purple. The colours are accurately represented in the chromolithographs. If the tissue has been hardened in formol-Müller, the sections show remarkably well the Nissl bodies in the cells. Another advantage of the method is that it lends itself to photomicrography. It is of importance to remember that the tissue will not take the carmine stain after it has been placed in spirit, and that also it does not answer with the Pal modification. Sections stained by the carmine method alone, or by the combination with the Weigert, are particularly valuable for examining both the ganglion cells and the neuroglia cells of the cortex cerebri. The combined method I have found useful, also, for staining peripheral nerves and endings.

Great care must be taken to obtain a carminate of soda, made from unadulterated carmine prepared from the male insect. *October 17th*, 1899.

16. *A case of Negro lethargy.*

By Stephen Mackenzie.

(With Plate VII.)

With a note on the histological changes of the nervous system; by Frederick W. Mott, F.R.S.

On November 14th, 1890, I exhibited a patient suffering from negro lethargy at a meeting of the Clinical Society, and the communication containing the particulars of the case was published in vol. xxiv of that Society's 'Transactions.'

In that paper the details of the necropsy were recorded, but not the microscopical changes. Dr. Mott, after communicating two cases of negro lethargy to this Society, inquired of me concerning the microscopical changes in my case. These, as far as the modes of staining allow of their being followed, are of a similar nature to those found in Dr. Mott's two cases, and as they have not been hitherto published it seemed desirable they should be recorded in the same volume of the Society's 'Transactions' as Dr. Mott's. My share of the communication consists in giving a *résumé* of the clinical records and necropsy. The value of the communication is entirely due to Dr. Mott's description of the histological changes.

Mandombe, a negro about twenty-two years of age, came from the Lower Congo, from a village that has been devastated by negro lethargy; his mother, two sisters and most of his relatives on both sides of his family died from the disease.

The symptoms of his fatal illness began about ten or eleven months before his death with persistent diarrhœa. This was followed by a feeling of dulness and heaviness. He came to England in June 1890. At this time he was comparatively vivacious, and presented no signs of organic disease. By October his mental and physical condition had markedly deteriorated. Drowsiness in the day-time had been increasing upon him, and he evinced a mental fatigue and lethargy that were striking. His motor power had become increasingly im-

paired. His gait was uncertain, feeble, and tremulous, there was tremor of the arms, he became feverish and began to pass urine unconsciously.

Mandombe was admitted into the London Hospital on October 6th, 1890. He presented the usual physiognomy and colour of the negro race. His body was moderately nourished, the skin dry, the mucous membranes of natural colour. His tongue was tremulous, rather dry, flabby, and indented by the teeth. The liver dulness commenced above at the seventh rib, and extended to the lower costal margin. He complained of pain in the lower part of right chest, and flinched when the liver was percussed. The abdomen measured 34¼ ins. in circumference, and there was a doubtful fluctuation wave. His pulse was 138, of fair force and regular. The heart's apex-beat in the sixth space, four inches from the mid-sternal line. No murmur audible, first sound at apex rather toneless. The lungs were normal except for a few râles at the bases. His conjunctivæ were injected; pupils of medium size, equal, and reacted to light. The retinal veins were large and dark, the edges of the papillæ well-defined. Examination of his blood showed 110 per cent. of coloured corpuscles, 70 per cent. of hæmoglobin, 1 colourless to 275 coloured corpuscles. Urine 1034, acid, albumen a trace, no sugar. His temperature was 101·3° F. on the morning of admission, but fell to 97° in the evening.

His general appearance on admission was not that of a person profoundly ill. He had been sleeping most of the time since his admission. When roused he appeared fairly intelligent and observant of what was going on around him. His conversation was practically limited to monosyllabic answers to questions. He did not seem reticent or morose, simply quiet or lethargic. His motor powers were very feeble; he walked in a tottering manner, and he was extremely tremulous, especially in the upper extremities and tongue. Cutaneous sensibility (to pin prick) was everywhere present. The knee-jerks were good, if anything rather glib; superficial reflexes present, no ankle clonus. Embryo *Filaria diurna* and *perstans* were found in his blood.

His condition between the time of his admission and December may be summarised. He was put on a nutritious diet, was given a warm bath each day, and ordered a saline diuretic,

with sulphate of magnesium. This, with occasional five-grain doses of quinine, is all the medicine, except aperients as required, he has taken. His mental condition has been slightly variable, but on the whole has progressively deteriorated. Frequent mention occurs in the notes of the patient being in a kind of stupor, and being "downcast." He rouses up at times, however, and appears to be interested in letters from home which have been read to him by the sister or nurse. He hardly ever converses with anyone spontaneously, but replies to questions put to him, usually slowly and in monosyllables. His condition is perhaps best described as one of lethargy or torpor.

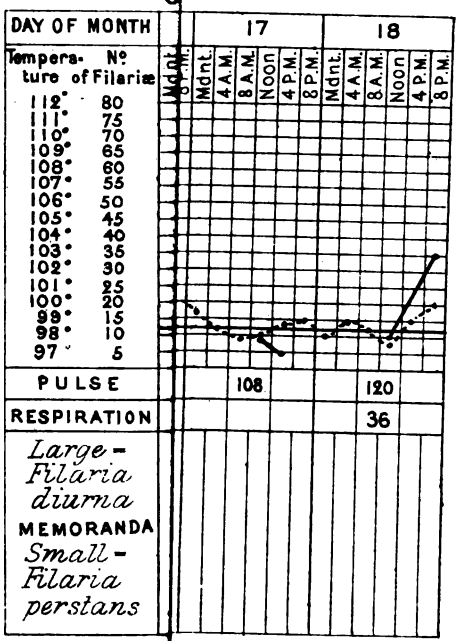
His muscular power is certainly feebler, so that he cannot sit up long without fatigue. Tremor has been a conspicuous feature of his case. It was very great when he first came to the hospital, just after he had been found in a state of insensibility, with high fever and profuse perspiration. He had such an attack on October 27th. He had a prolonged rigor, accompanied by extreme tremor, which remained increased after the rigor. His temperature, which had been nearly normal for some days, went up to 103°. His pulse was 120, respirations 32. His tongue was red, moist, and tooth-indented. The temperature came down the next day, but the tremor remained very great.

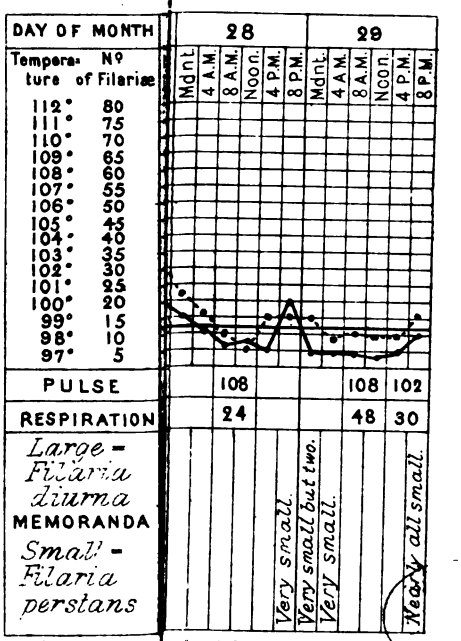
His temperature has been irregularly febrile, remittent in type, moderate in degree, and presenting no regularity in its exacerbations, but preserving the usual characteristic of evening maxima. His pulse is usually above 100, frequently 120, and has been as high as 144 and 150. No fresh signs have developed in his lungs. His tongue is exceedingly tremulous.

The urine contained a trace of albumen on the two first days of observation: never since. He now passes urine and fæces involuntarily. The patient has lost weight; admitted, he weighed 10 st. 1 lb.; on Oct. 19th, 9 st. 9 lbs.; and on Oct. 26th, 9 st. 5 lbs.

A bedsore, with a long and deep sinus, has formed over the sacrum. His gums have recently become soft and spongy and bleed readily. Breath offensive.

December 2nd.—The patient up to yesterday was in a lethargic condition, but becoming perceptibly weaker day by day. He





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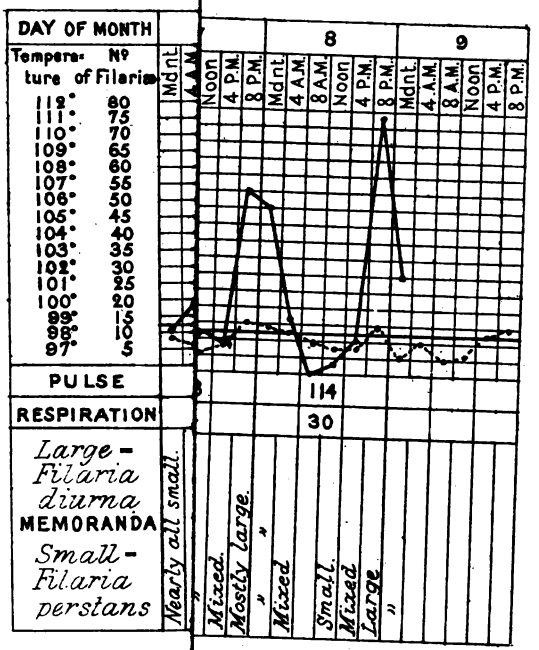

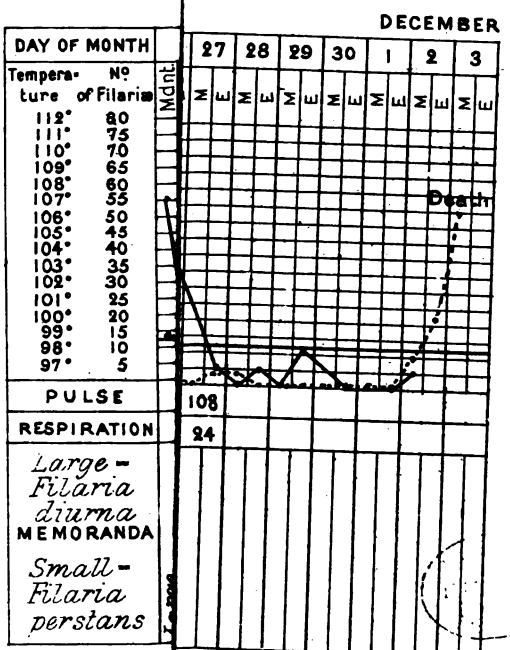

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has only spoken in monosyllables, or used simple phrases, such as "Good morning." Yesterday morning was noticed some difficulty in swallowing, and he put his hand to his throat during deglutition. On the evening of November 30th his head was a little retracted. Yesterday morning his head was more retracted, and has remained so. Attempts to flex it appear to cause pain. He is now, 3 P.M., lying with his head markedly retracted, and the body is twitched by convulsive movements. His breathing is jerky and irregular. Whilst observing him he was seized with spasm in the throat, and attempts to arouse him or to make him swallow brought on respiratory spasm. He lies with his eyes half open. The conjunctivæ are injected, his pupils $2\frac{1}{2}$ mm.; the eyes are fixed and directed a little upwards. The skin everywhere exceedingly dry. Plantar reflex and knee-jerk present. Sordes on lips and teeth. 9.30 P.M. —The spasms have become less noisy and frequent. Tracheal râles present. Pulse 160.

The breathing became irregular and weak, and muco-sanguinolent fluid was coughed up. Occasional convulsive attacks took place, and he died at 5.55 A.M. December 3rd.

His temperature the last few days had been subnormal (96°), but rose during the last day to normal, and steadily continued to rise from 8 P.M., when it was 101·6° to 106·8° at the time when death occurred.

The *autopsy* was made two and a half hours after death, with the assistance of Dr. Manson. The body was well nourished. Efforts were first made to find the parent worms of the *Filariæ*. Axillary and inguinal glands were dissected out, cut across, the fluid expressed and examined, but no *Filariæ* were found. The thoracic duct, receptaculum chyli, and abdominal lymphatics were carefully dissected out by Mr Dean, opened, and examined at various points. They presented no indications of disease, and no parent worms were found anywhere. The blood from the heart and the sinuses of the brain was collected and examined. That from each part contained abundant living embryo *Filaria diurna* and *perstans*. In the process of opening the spinal canal to examine the cord, small round or oval bodies were noticed in the dorsal muscles, which proved on microscopical examination to be encysted or vesicular parasites, and identified as the encysted stage of the *Tænia solium*, *Cysti-*

cercus cellulosæ. Examination of the muscles in various parts showed the presence of numbers of *Cysticerci*.

The *heart* presented no signs of disease. It weighed 10½ oz. The muscle of good colour. Valves and orifices healthy. All recesses and pouches were carefully examined for parent worms, with negative results.

Larynx.—The epiglottis and ary-epiglottic folds were œdematous, and this no doubt stood related to the difficulty of deglutition and respiratory spasm noticed during the last two days of life.

Lungs weighed each 10 oz.; they were healthy.

Liver 2 lbs. 13 oz.; slight sublobular congestion; no other sign of disease.

Spleen 7½ oz., firm and healthy.

Lymphatic glands.—Though no statement is made in the notes, I feel sure that the glands, which were carefully examined in many parts, were not enlarged as in Dr. Mott's cases.

Kidneys each weighed 6 oz., and showed no morbid changes.

Brain.—The sinuses were full of blood, and the veins of the pia mater distended. Membranes healthy. Brain substance firm, and presented no abnormal appearance, with one exception. It was carefully sliced in every direction, and on the under surface of the left frontal lobe one *Cysticercus cellulosæ* was discovered. No changes were noticed in the brain around it.

The *spinal cord* was examined throughout, but no naked-eye changes were observed.

The accompanying charts represent graphically the numeration of *Filariæ*, etc. at different hours of the day, for a period of several weeks.

Histological examination. By FREDERICK W. MOTT, F.R.S.

The specimens which were kindly sent to me by Dr. Mackenzie were sections of the brain, liver, heart, spleen and kidneys, cut with a freezing microtome, and stained with logwood and eosine. Some of the brain sections were also stained with carmine and blue black. No special stains for degeneration changes either in the nerve-cells or fibres had been employed; but the chronic *meningo-encephalitis*, as evidenced by the universal infiltration of

DESCRIPTION OF PLATE VII,

Illustrating the communication on a case of African Lethargy by Stephen Mackenzie and F. W. Mott, F.R.S. (Page 118.)

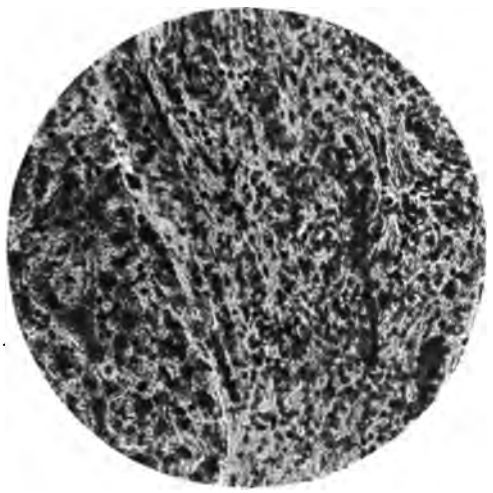
FIG. 1.—Section of the liver, showing on the left, atrophied hepatic cells, and on the right, chronic interstitial inflammation affecting the portal canal. Magnification 300.

FIG. 2.—Section of a small vessel of the occipital lobe, showing perivascular lymphatics filled with leucocytes. Magnification 300.

FIG. 3.—Section of the heart, showing a lymph space distended with mononuclear leucocytes. The fibres show no distinct transverse striation. Magnification 400.

FIG. 4.—Transverse section of a small vessel in the corpus striatum; the perivascular lymphatic is seen thickly filled with leucocytes. Magnification 500.

From microphotographs.



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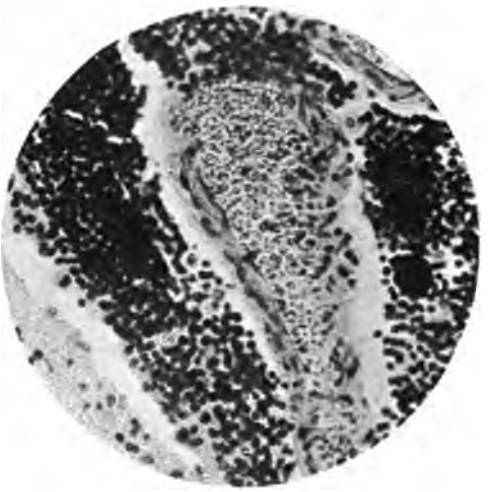

Fig. 2.

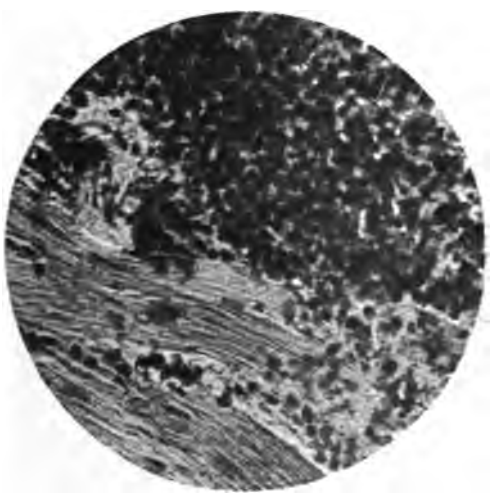

Fig. 3.

Fig. 4.

Bale & Danielsson, Ltd.

the pia-arachnoid and distension of the perivascular lymphatics of the brain with mononuclear leucocytes, was as intense as in the two cases previously described. The sections examined were from varied situations, such as the occipital lobe, the temporal lobe, and the corpus striatum, and all showed this same change, indicating a chronic inflammatory process (*vide* Pl. VII, figs. 2, 4).

Sections of the liver showed a chronic interstitial inflammation affecting the portal canal and its branches, though not equally throughout the organ. In some parts of the sections there are little clumps of mononuclear leucocytes, and where these are especially numerous the liver-cells appear somewhat atrophied and the protoplasm altered (*vide* Pl. VII, fig. 1). The kidneys presented no abnormal microscopical appearances, neither was there anything noteworthy in the spleen.

Sections of the heart showed œdema of the myocardium, the fibres being widely separated in places by distension of the lymph-spaces, and here there are clumps of leucocytes, mostly mononuclear, lying in the spaces (*vide* Pl. VII, fig. 3); probably this condition of œdema is to be associated with slow death from cardiac and respiratory failure.

Remarks.—The fact that this case shows *the same chronic meningo-encephalitis as the other two* is of importance in establishing this lesion as that of African lethargy, although the cause of the chronic inflammatory process has still to be discovered. The case is also of interest in the fact that the patient died with hyperpyrexia, and that nothing was found *post mortem* in the organs to account for it; hence it is probable that in Case 1, p. 107, the hyperpyrexia was due to the nervous affection and not to the small abscess in the lung. That is to say, we may consider hyperpyrexia as a symptom of the disease and not a complication.

The chronic interstitial inflammation of the liver is also of interest, because in one of the cases I have recorded this was found, though in a much less degree. I associated it with the inflammatory condition of the duodenum due to Anchylostoma, considering it probable that the parasites led to the absorption of some toxic irritant by the portal circulation. In this case of Dr. Mackenzie there are, however, no records of parasites in the intestines, so that such an argument cannot be applied to this case.

February 6th, 1900.

17. *Observations on the excretion of nitrogen in rheumatoid arthritis.*

By WILLIAM BAIN.

(From the Physiological Laboratory, Leeds.)

RECORDED observations on the excretion of the nitrogenous waste products in rheumatoid arthritis are very few in number. I have been unable to trace more than two references. Dr. Archibald Garrod in his treatise on rheumatism states that Dr. Angel Money has observed excessive variations in the amount of urea and uric acid excreted; and also that Drachmann has noted a diminution in the amount of phosphates; and secondly Von Jacksch makes a general statement to the effect that uric acid is diminished in chronic arthritis. With the hope of adding to our scanty knowledge, I have examined the urine of the following case of rheumatoid arthritis, and must thank Dr. Barrs for affording me the opportunity of doing so.

G. S—, a labourer, aged 27, was readmitted into the Leeds General Infirmary on September 25th, 1899, suffering from rheumatoid arthritis. He was a small delicate-looking man with the following past history:

Seven years previously he had injured his right knee, recovery following within a month; nevertheless he ascribed his immediate condition to that injury. Two years later the other knee became painful and gradually increased in size. Four years subsequently he was an in-patient under Dr. Barrs, when both knees were found to be affected, the right more than the left.

On readmission at the time of observation his condition was as follows:—The temporo-maxillary joint was slightly affected. Both ankle-joints were enlarged, the malleoli being chiefly affected, and movement was curtailed. The bases of the first and second metatarsal bones of the right foot were thickened. Both knee-joints were very much enlarged, especially the internal condyles of the femora. In the right, fluctuation could be detected and there was distinct lipping of the femur and patella. There was considerable wasting of muscles, the extensors of the knee being apparently more atrophied than the flexors. The right great

trochanter was enlarged, the left less markedly. In the hands there was some basal enlargement of all the middle phalanges. Marked wasting of the interossei muscles was noticeable with ulnar deviation of the digits. Finally both wrists, both elbows, and the spinous processes of the lumbar and lower dorsal vertebræ were involved. The urine was acid in reaction and free from albumen and albumose.

The analysis of the urine included the determination of the total daily excretion of urea, uric acid, P_2O_5, ammonia, purin bases and lactic acid.

Methods of analysis.—For the estimation of urea the hypobromite method was employed, a fresh solution being made each day. Both Hopkins's and Salkowski's methods were used for estimating uric acid, Schlösing's method for ammonia, and P_2O_5 by titration with uranium nitrate.

In estimating lactic acid, 1 c.c. of a 25 per cent. solution of sulphuric acid was added to 100 c.c. of urine, and then barium hydrate until no more precipitate appeared. The baryta was precipitated by passing a stream of carbonic acid gas through the solution, which was then filtered, and the filtrate evaporated to a thin syrup over a water-bath, the temperature of the bath not exceeding 70° C. About ten volumes of alcohol were gradually added to the syrupy fluid and then evaporated. This was repeated and afterwards dilute phosphoric acid added to the residue, which was then extracted for twenty-four hours with an excess of ether in Schwartz's apparatus. The ethereal solution having been evaporated, a watery solution of the residue was obtained, which was then submitted to Uffelmann's test.

To determine the alloxur bases, Salkowski's recent method was adopted; 600 c.c. of urine were taken, the phosphates having been precipitated by ammonium and magnesium mixture and removed by filtration. Three per cent. silver nitrate solution was then added (6 c.c. to 100 c.c. of the filtrate) and after brisk stirring the whole set aside for an hour in a dark place. After ascertaining that there was a sufficiency of silver present, the solution was filtered and the precipitate washed chlorine and silver free. The magnesium silver urate was then decomposed by passing H_2S in acid solution through it. The fluid was now heated, filtered, and evaporated to dryness on a water-bath. The residue was heated with about 30 c.c. of dilute sulphuric acid

brought to the boiling point, and left in a cool place for about twenty hours. The precipitate (uric acid) was then collected, washed with dilute sulphuric acid, dried and weighed. The filtrate and washings, amounting to about 50 c.c., were rendered ammoniacal, silver nitrate added, the precipitate so obtained was filtered, washed chlorine silver and sulphate free and then incinerated in a porcelain capsule. The ash obtained was extracted with nitric acid and the silver estimated by titration with ammonia sulpho-cyanate. From this silver determination the amount of alloxur base is calculated from the average amount of silver contained in the silver compounds of the different bases.

The patient was on the following diet for three days before beginning the examination of the urine.

Tea, 2 pints; bread and butter, 8 oz.; milk, 1 pint; dinner, 1½ lbs., including 4 oz. meat.

The results obtained by the methods described are here tabulated (see p. 127).

There are two points in the history of this case to which reference may be made. The first is the possibility of a causative relation between the injury and the disease. As a rule the influence of injury is more marked in the localised than in the poly-articular variety of the affection; and further the injured joint is usually the part where the disease first manifests itself. In this case the opposite knee was primarily involved. If there is any ætiological connection it is difficult in the case under consideration to understand the sequence of events, except on the hypothesis that the remote effects resulted from nervous perturbation. Such a supposition is not necessarily antagonistic to the theory of a microbic origin.

The second point is the effusion which was noticed in the right knee-joint. Some authorities, Senator for instance, affirm that the fluid contents of the articular cavity are never increased, but almost always diminished. This is a matter with regard to which most English and Continental authorities are at variance.

Regarding the examination of the urine there was a diminution in the excretion of uric acid and P_2O_5. It is stated that in healthy individuals the excretion of uric acid varies from ·3 to 1·2 grammes. Although I have examined the urine of a moderately

TABLE *showing the analytical details of the urine in the twenty-four hours.*

Date	Total Quantity in c.c.	Urea in grms.	Uric Acid in grms.	P_2O_5 in grms.	Alloxur Bases in grms.	Ammonia in grms.	Lactic Acid.
Oct 21.	1185	19·70	·228	·858	·027	·386	
" 22.	1040	20·80	·236	·926	·029	·300	
" 23.	1495	20·96	·294	1·04	·031	·430	Absent
" 24.	1300	18·2	·234	·912	·044	·265	Absent
" 25.	1150	16·675	·247	·940	·037	·275	Absent
" 26.	1140	18·24	·371	1·25	·041	·310	
" 27.	1340	17·42	·256	·977	·028	·810	Absent
Averages	1235	18·856	·266	·986	·033	·397	

large number of healthy people I have never met with an excretion below ·4 gramme. The normal relationship between the uric acid and alloxur bases was not disturbed.

As to the phosphates, they are reported to vary in health between wide limits, viz. from 1 to 8 grammes. It will be noted that the minimum was slightly exceeded, and as a further point of interest that the slight variation in their excretion closely followed that of the uric acid. *March 6th*, 1900.

18. A DISCUSSION ON THE PROTEIDS WHICH MAY OCCUR IN URINE.

(*February 20th and March 21st*, 1900.)

W. D. HALLIBURTON, F.R.S.

IT was with considerable hesitation that I consented to open here to-night a discussion on the subject of albuminuria. I beg to thank the Society for the honour they have done physiology in selecting me for such a responsible position. I, however, feel that one who is more in touch with the clinical aspect of the subject would have been altogether more suitable. Division of labour is nowadays necessary in science as well as in the arts and crafts, but specialisation, though it has obvious advantages, is always attended with disadvantages. The clinical observer has, as a rule, neither the time nor the laboratory in which to carry out chemical and experimental researches; on the other hand, the physiological investigator has seldom the opportunity or the energy to carry on simultaneously bedside observations. The new departures which the Pathological Society is now making with such marked success will do much, I am convinced, to reduce this disadvantage to a minimum; and a free interchange of opinions and intercourse between the two sections of workers is the only way in which medicine and the institutes of medicine may mutually benefit.

It was some such feeling as this that prompted me to accept the invitation so kindly proffered to me. The Society must, however, at the outset understand that all I shall attempt to do is to open the discussion, to set the ball a-rolling in the hope that if anything valuable does arise, it will do so in the later phases of the debate, for I fear that I cannot bring before you anything startling, or, indeed, anything which is new.

The whole subject of the proteids is one which always possessed for me a singular fascination; the feeling must resemble

that of an explorer in an unknown and mysterious new country. When the country is well explored, accurately mapped, and its mysteries discovered to be mere matters of fact, travel there is still pleasant, it is in fact easier, and may lead to more useful and lasting results. So, no doubt, it will be in time when chemists and physiologists have settled all the vexed questions concerning those compounds which we are discussing to-night, compounds which lie at the root of protoplasm, and the behaviour of which is the fundamental character of every vital action. At present, however, we are all groping in the dark, and so thick does the blackness sometimes appear that one would be tempted to retire from the field, were it not for the remembrance that the darkest hours are often those that precede the dawn. The many glimmers of light that are now continually breaking out from far and near laboratories do indeed indicate that the final conquest of organic chemistry cannot be very far distant. A glance at the past will show us that some advance has been made, and our knowledge now, compared with what it was say twenty years ago, may be seen by a glance at the text-books of the two periods. During this time the properties and distinctive characters of the albumoses or proteoses have been discovered; the nucleo-proteids have been born, and are growing into important units of the proteid fraternity; the histones, too, and the protamines have been more lately included in the same family.

There is hardly a single member of this large and growing tribe that has not at one time or another been found straying into foreign lands, and the presence of these strangers, who then may become active and dangerous foes, attracts particular attention and interest when they appear within the urine, owing to the breaking down of the first line of defence in the close array of the stalwart renal epithelium.

The proteids which most frequently break through the barrier are those which occupy the frontier country, the blood; and of these the twin brethren, serum albumin and serum globulin, are the commonest invaders. But in other cases the proteids came from more distant regions, such as those which are characteristic of digestive proteolysis, the proteoses and peptones; and if we study the literature of the subject we find cases recorded where even histones, an imperfectly-known race, and other rare specimens have been detected.

It is obvious that in an address of about thirty minutes duration one cannot do justice to all branches and aspects of so wide a subject, and so I propose to restrict what I have yet to say, first, to those proteids which most frequently occur in the urine, and secondly, to a brief allusion to a few of the more common of the rarer species. I shall also exclude from consideration, the necessary proteid contamination of the urine which occurs when the blood, owing to hæmorrhage, appears there, or when pus or semen are present. Although hæmoglobin is a proteid in the wider sense, I would suggest that the subject of hæmoglobinuria and the appearance in the urine of derivatives of the blood pigment should be excluded from the discussion.

We must, however, still devote a few more remarks of a preliminary nature to the question, Is any proteid present in normal urine? The problem has passed through as many vicissitudes as the corresponding question relating to presence of sugar in the normal secretion. Both have finally received an affirmative answer, but in both cases the quantity is so small that for all practical purposes normal urine may be considered to be free from both sugar and albumin. The most recent work on this subject has been performed by K. A. H. Mörner, of Stockholm. In order to obtain a quantity of the proteid sufficient to work with subsequently, it was necessary to use many hundred litres of normal human urine. One always suspects a source of fallacy when one hears of such vast quantities of urine; they must have been collected from numerous people, and although Mörner doubtless selected his subjects with the greatest care, there is always the possibility that one or more of them may have had, if not undetected kidney disease, at least a condition of slight temporary or functional albuminuria. If this was the case, of course the whole experiment was vitiated. While we bear this in mind, one cannot help feeling that Mörner's work is the only really thorough investigation yet published, and we are bound to accept his results until they are demonstrated to be incorrect. The amount of proteid is very small, averaging 0·003 per cent. The larger quantity of this is present in suspension in the ordinary mucous cloud or nubecula; from it he separated a specific number of the mucin group, which he calls urine-mucoid. The remainder of the proteid is in solution, and consists of traces of serum-albumin, together with a small quantity of a proteid pre-

cipitable by acetic acid. This consists of nucleo-proteid, and precipitated with it was a small quantity of chondroitin-sulphuric acid, a substance which up to that time had been found exclusively in cartilage. He does not adduce any proof as to how much of the proteid leaves the body by the kidney and how much by the urinary bladder and ducts. The presumption is that the greater part, including naturally the whole of the nubecula, originates from the mucous membrane of the urinary passages. In this connection we should also mention the substance which Bondzynski and Gottlieb call oxy-proteic acid. This they find to be a small but constant constituent of human and dogs' urine, and though it is not at present a very well characterised substance, it is doubtless an immediate proteid derivative, possibly an oxidation product.

From normal urine one passes naturally next to briefly consider what is called "physiological or functional albuminuria." I always feel inclined to object to the adjective physiological, for one must regard the conditions under which it occurs as being really pathological, even though the morbid condition is not a very serious one. The most marked condition in which this occurs is after prolonged muscular exercise. It is probable that vigorous muscular work in a certain proportion of people, variously given from 3 to 16 per cent. of those examined—it may be in those whose kidneys are below par,—will produce the albuminuria by causing a temporary congestion of the kidneys; experimentally we know that interference with the circulation through the kidneys lowers the activity of the kidney-cells, and so produces a leakage of albumin. A somewhat similar condition occurs in some people after the application of cold to the body, as after a cold bath; the blood is driven into the interior of the body from the skin, and the renal vessels are thus overfilled. In some cases, again, derangements of the nervous system (which interfere with the vaso-motor regulation of the kidney vessels) and derangements of digestion and anæmia (which alter temporarily the composition of the blood or lower the vitality of the renal cells) may lead to a similar albuminuric state. The pressure of tumours or of the pregnant uterus on the renal veins will cause albuminuria, as in experiments on animals in which the renal veins are compressed; venous congestion in heart disease will act in the same way. Various poisons introduced from with-

out, like phosphorus, or morphine, or manufactured within the body, as in typhoid fever, diphtheria, and other acute specific diseases, will lower the vitality of the renal epithelium, and so allow the serum-albumin of the blood to escape. In all these milder forms of albuminuria it is not without interest to note that the proteid which appears in greatest abundance, and sometimes exclusively, is the albumin and not the globulin of the blood.

When, however, we pass to real and serious cases of kidney disease, to truly pathological cases of albuminuria, we all but invariably find (in confirmation of Senator's original statement) that the so-called albumin is in reality a mixture of serum albumin with a varying proportion of serum globulin. The amount of the two proteids together rarely exceeds 1 per cent., though it may rise as high as 4 per cent. The relation of albumin to globulin has been a good deal investigated, but so far as we know at present the matter is mainly one of theoretical interest. The practical point a physician wishes to ascertain is whether or not there is in the urine a proteid which is coagulable by heat; both albumin and globulin are precipitated on heating the urine, and the size of the coagulum gives a rough indication of the amount of proteid present.

When I say that this question of the proportion of albumin to globulin has no practical interest, I hope I may not be misunderstood. For I believe that when the subject is more fully investigated, it will be found that there are definite laws that regulate the proportion, but the observations must be very numerous before these laws are discovered. At present the experiments which have been performed are in part vitiated by erroneous methods of analysis; and in part, where correct methods have been employed, the number of experiments has been too small. For these reasons different observers have contradicted each other, and the practical physician onlookers have exclaimed, "A plague on both your proteids, let us reckon them as one." Thus some have said that a high proportion of globulin indicates a waxy kidney, while others find that this is not invariably the case. One finds in the albuminuria that occurs in diabetes the proportion of albumin to globulin is a certain fraction, while subsequent observers' figures do not come anywhere near this; some have found that the albuminuria of heart disease is charac-

terised by a small, others by a large, proteid quotient. The term proteid quotient, it may be explained in passing, means the proportion of albumin to globulin.

Still, in spite of all these contradictions, certain facts do stand out as fairly certain, and though there are exceptions even to these rules, those cases can hardly be on all fours with the average cases of Bright's disease, but on seeking, probably some very exceptional condition either of the state of the kidney, the composition of the blood, the diet of the patient, or the method of the analysis, would be discoverable. The rules that may be laid down are the following:

1. That in the great majority of cases albumin is more abundant, often much more abundant, than globulin.

2. That this is much more marked in slight cases, and in cases of so-called physiological albuminuria than in severe cases.

3. That a high proportion of globulin usually indicates severe disease of the kidney.

4. That where both proteids are present there is usually found a rough correspondence between the proteid quotient of the blood and that of the urine.

5. That the proteid quotient of the blood is a very variable quantity. It varies in different animals, in the same animal or persons at different times, and such differences are not proved to be related to differences in the kind of nutriment ingested.

6. That the proteid quotient in the urine is still more variable than that in the blood, and that these variations do not necessarily correspond to variations in the proteid quotient of the blood.

These can hardly be called rules, but even to these there are exceptions; thus one will sometimes find, even in an apparently mild case, that the amount of globulin exceeds that of albumin, and occasionally one may find that albumin is absent, and globulin the only proteid present. This was so in one case out of forty examined by Hammarsten. It was also so in the well-known case published by Byrom Bramwell and Noël Paton, in which a globulin was curiously enough separated in a crystalline form. Albumins have been frequently crystallised, but this is the only hitherto recorded instance in which a globulin has been

obtained either spontaneously or artificially in a crystalline condition.

But if we consider the general rule rather than the exceptions, how do we account for the fact that albumin is so much more abundant in the urine than globulin? In answering such a question two obvious courses are open to one; one may say that it is due to the vital action of the kidney cells. This explanation is no explanation at all; it is merely a confession that we do not understand it, and can never hope to understand it, but we will shelter ourselves beneath a mystic expression. The other course is to attempt to find an explanation on chemico-physical grounds. From this standpoint we must regard the leakage of proteid from the blood or lymph into the urine as due to physical factors —first, the pressure exercised by the blood on the renal epithelium; secondly, the permeability of the renal cells; and thirdly, the size of the molecules that pass through. When the kidney cells are in a healthy state they are practically impermeable to the large molecules of the blood proteids. When they are damaged, especially if the blood-pressure is high, they will let the proteid molecules through. But they will let through in larger quantity the smaller proteid molecules in preference to the larger ones. It has been shown by some very careful experiments by Gottwalt, which were confirmed by Noël Paton, that serum albumin passes under pressure through membranes more readily than serum globulin does. It is, therefore, not at all surprising to find that in normal urine the only blood-proteid present, and that in mere traces, is serum albumin; that in cases of mild or so-called physiological albuminuria the amount of globulin is almost negligible; and that it is not until the kidney cells are so injured by chronic disease, or by a severe acute attack, that the amount of globulin becomes considerable.

If we pursue the same line of argument we may next proceed to an examination of a new question, which is this:—In the blood-plasma the proteids in solution fall into two categories—(1) the serum albumin (or serum albumins, for there are probably several) comprises the proteids soluble in water, coagulable by heat, and non-precipitable by saturation with such a neutral salt as magnesium sulphate: (2) the globulins; these are also coagulable by heat, but are insoluble in water, and readily precipitable by excess of various neutral salts. They are two in

number; one of them, present in largest quantity, is the serum globulin we have just been talking about; the other is the mother substance of fibrin, and is called fibrinogen. The question to which we have been leading up is, Why does fibrinogen hardly ever pass into the urine? I imagine different people would answer this question in very different ways. Some might say that there is such a little fibrinogen in the blood (only 0·3 out of a total proteid percentage of 8) that if it passed into the urine it might escape detection, being masked by the relatively large amount of other proteids present. In answer to this I would reply that when fibrinogen is present, especially if it becomes converted into fibrin in the urine, its existence is unmistakable. Others might deny my premises altogether, and say that fibrinogen is often present; they would point to work by Lauder Brunton and D'Arcy Power, by Führy-Snethlage, by Gerhardt and by Pohl, who found in many specimens of albuminous urine a proteid coagulated by heat at the low temperature of 56° C. In answer to this I would point out that the mere coagulation temperature of a proteid is a most untrustworthy guide to its identity. I think I may speak with some authority on this subject. In its proper place, and in combination with other reactions, coagulation temperature has its proper value, but it varies greatly for the same proteid under varying conditions. The boiling point of water is 100° C.; this is a fairly fixed quantity; but take the water up a mountain and it no longer boils at 100° C., the conditions of the observation having been changed. In the case of proteids, no doubt their coagulation temperature is a fixed point under the same conditions; the difficulty is to get the conditions the same, for slight variations in the composition and concentration of the fluid in which they are dissolved will shift the coagulating point tremendously.

I of course know that cases of fibrinuria do occur sometimes, and there is, also, but little doubt that the substratum of a urinary cast is a slow formation of fibrin from fibrinogen, which exudes slowly through the walls of the damaged tubules; but the main contention with which I started appears to be indisputable, that fibrinogen is generally absent in the urine in cases where the other blood-proteids are present.

I should be inclined to explain this by an extension of the theory concerning molecular size. Though the size of the

fibrinogen molecule has not been accurately gauged, I gather from *a priori* considerations that it must exceed that of the other blood-proteids. When some does pass through, the renal epithelium is in a very bad way and we get urinary casts; when more passes through, so as to cause a clot of fibrin throughout the urine, the damage to the kidney is even more severe; thus we see it sometimes in chyluria, where the kidney or the urinary passages are pervious not only to big molecules of proteid, but even to microscopically visible particles of fat. We get it after the administration of cantharides, when the kidney bleeds; we get it in certain growths of the bladder, which naturally give rise to a lymph-like exudation from their surface; and we get it sometimes, as in a case recorded by Dr. D. M. Greig, of Dundee, where there is an exudation of liquor sanguinis in the kidney itself.

I should lay it down as a general rule, that in proteid substances the molecular size varies directly as its readiness of precipitation by neutral salts or by alcohol, and indirectly as its temperature of heat coagulation. If we contrast the proteids with the carbohydrates, we there find much the same state of things; the colloid carbohydrates, starch and glycogen, are substances with heavy molecules, and they are readily precipitable by neutral salts and by alcohol; the crystalline carbohydrates, like the sugars, have small molecules and are not precipitable by either group of reagents; the dextrins have molecules of intermediate size, and their precipitability is also intermediate in degree.

I know it is always risky to prophesy about anything in physiology; I hope some day to have time to put my ideas to the test of experiment, and so confirm or correct them. At present it is merely a working hypothesis to consider that the low coagulation temperature of fibrinogen, the readiness with which it can be salted out from solutions, and its tendency to pass into an insoluble condition (fibrin) with slight provocation, are all indications of its extreme colloidal nature; and that the comparative rarity or scarcity of its appearance in the urine, even when the other blood-proteids can traverse the renal cells, is readily explicable on the ground of the huge size of its molecules.

Now let us pass with a leap from the heaviest to the lightest

proteids, and briefly consider the principal known facts in relation to the appearance in the urine of the proteoses and peptones.

It is well known that although these substances are formed in the alimentary canal, they do not pass as such into the blood. Even during the active digestion of the most succulent of beef-steaks, not a trace of proteose or peptone is found either in the portal blood or in the lymph, still less in the urine. The columnar epithelium that lines the alimentary canal is the agent by which the harmful peptone or proteose is regenerated or synthesised into the useful albumin and globulin. In diseases of the alimentary canal in which this lining membrane is disintegrated or diseased, it seems possible that some of the morbid symptoms might be accounted for by supposing that the poisonous products of proteolysis pass through into the blood. If this is so, they should leave the body by the urine, for if in animals "peptone" is injected into the circulation it is not wholly utilised, but is in great measure cast out as a foreign substance by the kidneys. I have long been on the look out, both in urines submitted to me and in current literature, but have never yet come across a well-attested case of this kind; even in cholera and other severe forms of intestinal trouble, peptonuria does not appear to have been noticed. It is possible in such cases where the epithelium has vanished, the lymph cells beneath it may form a second line of defence, and carry out what they do not appear to do under normal circumstances, namely, the "regeneration of albumin."

Still peptonuria does occur, and the proteolysis that leads to the formation of the peptone does not occur within the alimentary canal, but in the tissues or in new growths, and here micro-organisms are the digestive agents. The condition occurs in a great variety of diseases, but the majority are those in which suppuration is a prominent pathological process.

Though one still uses the term peptonuria, it is now recognised that peptone in the correct sense of the term is hardly ever or never found. Urinary peptone is one of the proteoses, namely, deutero-proteose, which is the proteose nearest to the peptones, both in its reactions and its method of formation.

When true peptone is injected into the blood it appears as such in the urine. When deutero-proteose is injected into the blood

of carnivorous animals it appears in the urine as peptone; this is not found to be the case with herbivorous animals like rabbits. The carnivorous urine is rich in pepsin, but such urine produces no further digestive action when mixed with proteoses, first, because free acid is absent, and secondly, because many of the salts of urine exert an inhibitory influence on the ferment. Neumeister suggests that the change occurs in the act of secretion, when there is a momentary occurrence of free acid.

The human being appears in this particular to resemble the rabbit rather than the dog. If any proteolytic action occurs in the kidney itself converting primary proteoses into secondary (*i. e.* deutero-) proteoses, the action does not proceed so far as to lead to the formation of true peptone.

We must distinguish next between this condition which may still be called peptonuria, and the condition generally termed albumosuria. The condition was first described by Bence Jones, and the proteid is still often labelled Bence Jones albumin. This is a very rare condition, and the characters of the proteid are closely akin to, though not absolutely identical with, those of Kühne's hetero-proteose, one of the primary proteoses, distinguished from the other primary proteose, proto-proteose, by its insolubility in pure water. There have only been about a dozen cases of this condition which have been adequately described. They were nearly all in males, and in three cases the disease was osteomalacia. In Ribbink's case there was a sarcomatous growth in bones and other parts; the marrow was red and jelly-like, and the bones exhibited osteoporosis. In other cases, again, the disease was multiple myeloma of the bones. In all cases bone disease of one kind or another was present. A full description of the urine in five of these cases is given in the last edition of Neubauer and Vogel's *Analyse des Harns*, and what the reader will perhaps be most struck with are the differences in the character of the proteid in the various cases. I think this is in part to be explained by the admixture of the albumose (or globulose as Kühne appears to think it was in his case) with nucleo-proteid; some of the analyses certainly show the presence of phosphorus.

Huppert, who is the editor of the last edition of the book just mentioned, includes a sixth case, namely, that of Byrom Bramwell and Noël Paton. This was not a case of bone disease, and the

proteid of the urine was globulin in a crystalline form. It is curious that this mistake should have occurred. Huppert concluded the proteid was hetero-proteose on entirely insufficient grounds, namely on *a priori* reasoning from Noël Paton's paper. When he actually examined the proteid sent to him by Noël Paton he admitted the accuracy of Paton's description, and withdrew his previous opinion. I suppose this was too late for him to include it in the work on urinary analysis which he edited.

I understand, however, that other instances of this curious condition are to be brought before us this evening. Dr. Hutchison brought before the Physiological Society a short time ago a preliminary account of his case.[1] So far as my memory serves me, it was a case of bone disease (sarcoma) and the urinary proteid, though presenting some puzzling characters, agreed on the whole with the hetero-proteose of other observers. Dr. Bradshaw's case was also one of bone disease (myeloma); here, again, the proteose, though nearest in its reactions to hetero-proteose, possessed some characteristic features of its own.[2]

I have now nearly completed what I have to say. I have not attempted to do more than present an outline sketch of the subject. I have endeavoured to mention the principal proteids that may pass under abnormal circumstances into the urine, and have alluded to one or two which seldom make their appearance there. Under this last head I should like to include caseinogen. It is well known that lactose is frequently to be found in the urine during lactation. It is perhaps not remarkable that caseinogen, the other main characteristic constituent of milk, should be conspicuous for its absence, for of all known proteids in which the question has been specially investigated, caseinogen is the most indiffusible; it will not pass, unless its molecular aggregates have been broken up by the use of an alkali, like soda, through the pores of a Chamberland filter under pressures which permit the pressure-filtration of egg albumin, serum albumin, or even of the serum globulin of some animals (D. F. Harris).

The clinical significance of albumin and other proteids in the urine I have hardly endeavoured to touch, merely because I have not felt confidence in my ability to do so with the justice such an important subject demands. I hope, however, that this will not lead others to follow my example in the discussion. As

[1] See p. 146. [2] See p. 140.

I stated at the outset, the usefulness of a debate such as this will be greatly impaired if the pathologists of the bedside do not compare notes with the workers in the laboratory.

I have also purposely avoided any description of methods of analysis. I have felt it necessary to do this merely from considerations of time. It will, however, be useful if we could hear what tests are nowadays considered the most trustworthy. A new test for albumin in urine is one of the most frequent headings of papers on albuminuria, and it has been my fate to examine a large number of these new tests. Although I am not naturally conservative, I feel bound to say that in my experience this is a case where the old is the best. I consider that as general working tests, and those that one can absolutely trust, nothing can beat the time-honoured boiling test after acidulation with acetic (not nitric) acid, and Heller's well-known nitric acid reaction. Special cases of the rarer proteids naturally must be examined by all the modern armament of recent methods and latest knowledge. But it is always the common cases that possess the most important interest to the practitioner, and though the intelligent physician is always on the look out for the rare cases, it is one of the disappointments of life to discover how seldom they arise.

I hope what I have been able to say will form a stimulus to those who follow me to say something more interesting, and in sitting down I have again to express my gratitude to the Society for giving me the opportunity of placing my ideas on proteids in the urine in a consecutive manner before such an important section of the medical profession.

ROBERT BRADSHAW.

The contribution which, in response to your kind invitation, I have the honour to make to this discussion, will deal with the forms and significance of the proteids which appear in the urine in the condition which I have proposed to call myelopathic albumosuria.

Of this condition eleven well-marked instances are on record, and it was my good fortune to have under observation the only

authenticated case that has been met with in Great Britain since the one which was investigated by Dr. Macintyre more than fifty years ago, and from which all our knowledge of the subject begins.

The clinical aspect of my case has been dealt with so fully elsewhere[1] that I need not now dwell upon it. The patient was a man seventy years of age. During the last year of his life his urine is known to have presented the characters which are about to be described, and there are good reasons to suppose that they were present for a much longer time. During the last six or seven months of life there were indications of a profound change taking place in the osseous system, and the autopsy showed extensive changes in the bones of the trunk, which have been elsewhere described, while the kidneys did not show any striking departure from the normal.

The patient's attention was first drawn to his condition by his noticing that from time to time he voided urine which looked like milk. Of this I show you a specimen, and I think you will agree with me that its appearance is remarkable. When it is left to stand the substance which causes the opacity settles down, forming a mass not unlike the curds in butter-milk. This deposit often occupied a fourth or more of the bottle.

At other times the urine was clear, presenting nothing abnormal to the eye, except that it was remarkably viscid, and formed an abundant and persistent froth when shaken.

When it is heated carefully in a water-bath a dense white precipitate forms, and is seen to be complete at about 58° C. Precipitation generally begins at a lower temperature; the stronger the acidity, within limits, the earlier does it appear. I have seen it begin at a temperature several degrees below that of the body. Its appearance is hastened by agitating the fluid. If the reaction is alkaline it does not appear at all. Heating above 60° causes no further precipitation; on the contrary, some of the precipitate already formed is dissolved on boiling.

Treated with cold concentrated nitric acid it yields an abundant precipitate. If the specimen is now boiled, care being taken to break up the dense masses of coagulum which are sometimes formed, the precipitate almost entirely dissolves, but reappears on cooling.

[1] See references on p. 145 (1, 2).

Treatment with concentrated hydrochloric acid gives rise to a remarkably dense precipitate, which reacts to heat in the same way as that produced by nitric acid. Hydrochloric acid is a very delicate test for the body which we are considering, and gives a precipitate even when the urine has been largely diluted with water. I have seen a distinct turbidity appear with this reagent when the urine has been diluted with thirty volumes of water.

Brought in contact with a solution of ferrocyanide of potassium and acetic acid, no turbidity is produced at first unless a large excess of acid is added. On standing for ten or fifteen minutes, however, a moderate amount of turbidity gradually comes on, increasing till it forms a distinct precipitate, which is also to a great extent dissolved on boiling. The precipitate or coagulum caused by heat seems to be identical with the deposit, which was turbid when it was passed. Both these substances are insoluble in cold distilled water, but are entirely and rapidly dissolved by a weak solution of caustic soda in the cold, a watery solution of one part of the alkali in 1000 being sufficient. If the solution thus obtained is made faintly acid with acetic acid nearly all the proteid remains in solution, but is thrown down by heat and gives the characteristic albumose reaction with nitric acid. In fact the precipitated proteid seems to dissolve in weak alkaline fluids without undergoing any change of nature, at least it seems to behave in the same way as the proteid which has not been precipitated at all.[1]

The proportion of proteid present varied at different times, but was always large. I made a great number of estimations of it. The lowest proportion was 6 parts of dry proteid per 1000, the highest was 22 per 1000, a proportion approaching that found in many inflammatory effusions.

The principal reactions which I have described, and which serve to distinguish the body here present from the proteids commonly met with in pathological urine, may be thus indicated in tabular form.

[1] This statement is, however, only true with respect to a perfectly fresh solution. After the weak alkaline solution has been left to stand for a few hours neutralisation produces an abundant precipitation. Evidently the alkali first effects solution of the precipitated proteid, and subsequently slowly changes it into an albumosate.

Reagent.	Albumin.	Albumose.
Heat	Coagulum at 70° C. not soluble at 100° C.	Coagulum at 58° C. partly dissolved at 100° C.
Nitric acid.....	Coagulum, not soluble at 100° C.	Coagulum soluble at 100° C.
Hydrochloric acid	Slight coagulum	Dense coagulum.
Ferrocyanide of potassium and acetic acid	Dense coagulum	Coagulum slight, and comes on slowly.

I have not spoken of the biuret reaction because, after many trials, I am convinced that, contrary to what is generally taught, it affords no indication by which we can distinguish between albumens and globulins on the one hand, and albumoses and peptones on the other.

I have made several attempts to obtain the substance in question in solution free from the salts and other bodies associated with it in the urine, relying chiefly on the removal of salts by dialysis and precipitation of the proteids by absolute alcohol. The precipitate thus obtained is readily dissolved in distilled water. To obtain the substance pure Professor Neumeister recommends a somewhat tedious process which has been employed by Dr. Matthes under his direction, but which has not yielded satisfactory results in my hands. The method seems to me to be open to the objection that the treatment with hydrochloric acid at boiling heat, which is part of the process, may effect some permanent chemical change in the substance which it is proposed to isolate. Neumeister asserts that the pure substance will not coagulate when heated unless the solution has an acid reaction, and also contains salts, and my experiments with the substance obtained in relatively pure solution in the way I have described seem to confirm this statement.(3)

As far as I can make out only one kind of proteid was constantly present in the urine, at least in anything more than a trace. Serum albumen was scarcely ever present until near the end of the case, and as a rule all the proteid was thrown down at a temperature of 60°. No appreciable amount passes through a dialyser, neither does any precipitate take place when the

salts have been dialysed out. None of it is precipitated by saturating its neutral solution with magnesium sulphate, but saturation with ammonium sulphate removes it all. The fact that on boiling with nitric acid only part, though a large part, of the precipitate is dissolved may, I think, be explained by the influence of the salts present and by the deficiency of water.

To what class of bodies does this substance belong, and can we identify it with any other body known to physiological chemistry? To the first part of the question we can scarcely hesitate to reply that it is an albumose, for it gives in a marked degree the reaction with nitric acid which we have long regarded as distinctive of this class of bodies. To the second part of the question we are scarcely yet in a position to give a categorical reply, but most probably we shall be right if we answer in the negative. Among the different known albumoses hetero-albumose is that which most closely resembles the substance we have been considering, but as to the properties of hetero-albumose authorities are by no means entirely agreed. It is commonly stated that it is precipitated at 65°,(4) but Neumeister declares that none of the albumoses are "coagulated" by heat, and says nothing about their precipitation by that means.(5)

All authorities are, however, agreed that, unlike the body we are now considering, hetero-albumose is insoluble in distilled water.

The balance of evidence seems to me to be in favour of the conclusion to which Matthes and Neumeister have come, namely, that the albumose found in the urine in cases of this nature is a body of a peculiar kind, distinct from any substance which has been met with under any other circumstances, and this conclusion seems to me to be *a priori* the more probable from what we know of the morbid conditions under which the body is found.

I have here in tabular form a list of all the authentic cases in which this form of albumosuria has been recognised. In the great majority some affection of the bones was found either during life or after death, and in not one was the existence of bone disease positively excluded. In all the cases in which a complete microscopical examination was made, the morbid condition consisted of the invasion of the marrow spaces of the bones of the trunk by a cell formation, which replaced the red marrow and led to absorption of the hard structures of the bone.

It is difficult to avoid the inference that the albumose in the urine had its origin in the cell infiltration, but by what means it was formed we have no data on which to form an opinion. Whether a similar affection of the bones can exist without the occurrence of albumosuria is at present undecided.

To sum up. The experience of the last few years has shown that we must include in our symptomatology a specific well-defined condition of the urine, which for convenience we may call "myelopathic albumosuria," and that this condition is the earliest available indication of the existence of a grave and hitherto irremediable affection of the osseous system, an affection which, so far as we know, invariably proceeds to a fatal result.

Tabulated list of cases in which "Bence Jones" albumose has been observed in the urine ("Myelopathic albumosuria").

No.	Date of publication.	Observer.	Diagnosis during life.	Condition found at autopsy.
1	1847	Macintyre and Bence Jones (London) (6, 7, 8)	?	Mollities ossium rubra; description corresponds to multiple myeloma.
2	1883	Kühne (9)	Osteomalacia	Autopsy not obtained.
3	1889	Kahler (Prague) (10)	„	Multiple myeloma.
4	1891	Stokvis (Amsterdam) (11)	?	Bones brittle; marrow replaced by a red gelatinous mass.
5	1895	Stintzing (Jena) (12)	Osteomalacia	Multiple myeloma.
6	1897	Senator (Berlin) (13)	Nephritis, with albumosuria	Myelogenous round-celled sarcoma.
7	1897	Bozzolo (Turin) (14)	"Kahler's disease"	No record.
8	1898	Nannyn (Strasburg) (15)	Multiple myeloma	No record.
9	1898	Bradshaw (Liverpool)	Multiple myeloma	Multiple myeloma.
10	1899	Ellinger (Königsberg) (16)	None made	Multiple myeloma.
11	Not yet published	Fitz (Boston, U.S.A.)	Multiple myeloma	Multiple myeloma.

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ROBERT HUTCHISON

described a proteid found in the urine of a man who died in the London Hospital with multiple sarcomata affecting the marrow of the femur, tibia, ribs, and vertebræ. The diagnosis was verified by *post-mortem* examination.

The urine in this case was pale, slightly alkaline in reaction, somewhat more viscid than normal, with a specific gravity of 1018. About 900 c.c. were passed daily, containing 6 gr. of proteid (estimated by coagulation and weighing). On heating the urine, after rendering it faintly acid, opalescence appeared at 45°, and at 58° C. a flocculent precipitate separated out. On boiling this it gathered into a sticky lump, which floated to the surface but did not dissolve. Heller's test gave the usual ring, which was not affected by heat. The urine gave also all the usual proteid reactions, but the precipitate with ferro-

cyanide of potassium and acetic acid only appeared slowly. The coagulum produced by boiling re-dissolved very readily on the addition of dilute alkali. The proteid was precipitated by saturation with common salt in the presence of acetic acid, but not by salt alone, nor by magnesium sulphate, nor on half saturation with ammonium sulphate. It was separated by complete saturation with the latter salt, re-dissolved, purified by dialysis, and the above reactions confirmed. If a good deal of acetic acid was added it was found that the substance separated out at a temperature of about 45° C. It left no residue of nuclein on hydrolysis, nor did it yield any reducing substance. It contained no phosphorus, nor did it give any precipitate with ammonia, either alone or in presence of ammonium chloride. The conclusion was arrived at that the proteid in this case belonged to the class of albumens, but differed from all those hitherto described in the lowness of its coagulation point (58° C.). In this respect it resembled Bence Jones's albumose, but differed from it in being insoluble on boiling, and in its behaviour to nitric acid. It was also peculiar in the reluctance with which it was precipitated by acetic acid and ferrocyanide of potassium, and in the readiness with which the coagulum produced by boiling re-dissolved in dilute alkali. In addition to this proteid the urine contained a trace of globulin. A few fragmentary granular casts were also present. No chemical examination of the blood or tumours could be made. Microscopically the tumours were composed of large round cells, many of them containing coarse eosinophile granules.

W. Pavy, F.R.S.

In rising to take part in this discussion I will in the first place say that I am sure we must all of us feel under a debt of gratitude to Prof. Halliburton for the masterly way in which he has introduced the subject he has brought forward. No one is more qualified to speak authoritatively upon the subject of proteids than Prof. Halliburton, and we may consider that we are fortunate in having him here this evening in the position he holds. The first matter to consider is what is the condition of healthy urine. Does albumen, which is so exten-

sively met with under various circumstances, form a constituent of normal urine? I myself think that it does not, and I do not therefore consider it right to speak of physiological albuminuria. With the term functional albuminuria it is otherwise. We may have a functional condition quite distinct from any structural disease of the kidney, giving rise to the presence of albumen in the urine; but because functional, it does not follow that it is physiological.

I will not follow Prof. Halliburton into the point as to whether sugar is a constituent of healthy urine further than to touch upon the underlying principle standing in relation to the escape of albumen and sugar. Whilst I hold that albumen does not normally pass from the blood into the urine, I have always strenuously maintained that sugar does. The position of the two bodies from a physical point of view is essentially different. We have in the one case a colloid and in the other a crystalloid to deal with. A colloid, on account of the large size of its molecules, is not permitted to pass through membranes that freely give passage to the small molecules of which crystalloids are composed. In the circulation under natural circumstances through the kidney, the membranous walls of the vessels do not I would say permit of the permeation of the large molecules of which albumen consists, but we know that they do permit other smaller-sized molecules to pass. We know that the molecules of water pass, and if they permit these to pass I do not see how molecules not greatly differing in size can be held back. Upon this principle, whatever action may be subsequently exerted by the cells of the uriniferous tubules, I should think that all such small-sized molecular bodies as sugar, urea, and salts must pass with the water that escapes through the capillaries of the Malpighian tuft.

Pressure, as is known, exerts a modifying influence on passage through membranes, and what is observed is consistent with albumen finding its way into the urine under certain states of the circulation, and not doing so under natural circumstances. In experiments conducted outside the body it is noticeable when an albuminous liquid is placed on one side of a membrane and a saline solution on the other, that the saline matter passes through and mixes with the albuminous liquid, but that the albumen does not find its way through into the saline solution. By pressure the

result is altered, and under its influence albumen is observed to pass. Even with a Pasteur-Chamberland filter as the septum, which must have exceedingly fine pores, the albumen molecules under the influence of very great pressure may be made, as has been stated by Professor Halliburton, to pass.

We thus see that size of molecule and pressure are important factors in connection with the point under consideration. It is quite permissible to conceive that whilst bodies possessing a small molecular constitution readily pass from the blood into the urine, others, like albumen, built up into large molecules, fail to do so under a normal state of the circulation, but do so under an altered state, attended with increased pressure within the vessels.

I have given grounds for healthy urine being free from albumen, and in confirmation, although our tests for albumen are superlatively sensitive, none is susceptible of recognition. But are we to consider perfectly healthy urine as devoid of proteids? No, for the reason that from the urinary tract below the kidney proteid matter is thrown off in the secretion coming from the mucous surface. Nucleo-albumen or mucin is the principle that we have here to deal with. Ordinarily it is not present to an extent to give any trouble in testing for albumen, but it sometimes happens to exist in sufficient quantity to be perceptibly thrown down as a precipitate, and then, unless care is taken, may be mistaken for albumen. Instances from time to time occur in which this error is committed in connection with life assurance cases.

Proteid may appear in the urine in the form of peptone and albumose. Notwithstanding that peptone and albumose are so extensively produced as results of digestion, peptonuria and albumosuria are but of somewhat rare occurrence. We take proteid food. In the state in which it is taken it is not in a position to be serviceable to us. Its molecules are too large to pass from the alimentary canal into the circulatory system. It becomes broken down into peptone and albumose, which are bodies of smaller molecular constitution, and now absorption can occur. As a next step, these become re-constructed into higher proteid, and so completely is the synthesising process carried out that the bodies to be synthesised fail as such to reach the circulation, and thus are precluded from reaching the kidney. It is possible,

however, through error, that peptone and albumose from an alimentary source may reach the kidney, but peptonuria and albumosuria are usually found to be associated with morbid states of the system in which a special kind of breaking down of proteid matter is going on. The fact of peptone and albumose constituting digestion products intended for absorption shows that they stand, in connection with passage through a membrane, in an altogether different position from albumen. When existing in the blood, on account of their diffusibility, they may be looked for to reach the urine without any fault on the part of the kidney.

We have albumen and globulin to deal with in the blood, and both are found to get into the urine. I noticed the remark of Prof. Halliburton that albumen is usually found in larger quantity than globulin in the urine, and he also observed that albumen is more diffusible than globulin. This is in harmony with what might be expected upon the principle of the result being influenced by relative diffusibility. I do not know of the relative amount of these bodies having any bearing of clinical significance.

Albumen and globulin are the bodies met with in the albuminuria of ordinary renal disease. They are also the bodies met with in the transient forms of the condition occurring as a result it may be of simple congestion from causes existing elsewhere, of food ingestion, cold bathing, and muscular exertion.

The same, as far as I know, is to be said in relation to functional cyclic albuminuria; but here I may mention that I have sometimes noticed a certain amount of precipitate produced by an organic acid, as occurs with mucin and a nucleo-proteid. At the same time there has been nothing visible to point to anything unusual with regard to mucus. In using, for instance, the acetic or citric acid and ferrocyanide of potassium test, which, properly employed, I look upon as not to be excelled, a certain amount of precipitate becomes evident, and grows on the addition of the acid, which, of course, is not albumen. It is the precipitate that falls on the addition of the ferrocyanide that consists of albumen.

Cyclic albuminuria strikingly, I consider, fits in with what I have said about the influence of vascular pressure. A person after passing the night in the recumbent position, rises in the

morning, and subsequently goes through his daily avocations. At the time of rising his urine is found to be free from albumen, but later on in the forenoon albumen, sometimes in marked amount, is discoverable. That this is not due to his breakfast is shown by no albumen appearing if he breakfasts and remains in bed. As a rule the albumen diminishes as the day goes on, and more frequently than not it is absent at the time of going to bed. The next day the same round of events occurs, and this may go on not only week after week and month after month, but even year after year, without leading to anything further. In no instance which after careful examination could be definitely pronounced at the beginning to be a true functional cyclic case, have I ever known the condition to pass on into renal disease.

Now are we not justified in looking to the state of the vascular system for the explanation of these phenomena? The subjects of this condition are of a mobile nature, with lax arteries and a sharply-acting heart, giving rise to a very perceptible smacking impulse. The night is passed in the recumbent position, which may be taken to be the one in which there is the least blood-pressure within the vessels of the kidney. By the upright position assumed on rising the blood-pressure can scarcely fail to be altered, and in these subjects, through the lax state of vessels, it may become sufficient within the capillaries to lead to the albumen molecules passing out. At all events, it is indisputable that position of body is the determining factor of the variation noticed with regard to the condition of the urine in relation to albumen. There is in my mind an interesting case from the Middlesex Hospital, which was placed on record some years ago by Dr. Coupland. The usual difference had existed between the urine passed on rising in the morning and a few hours later on. The patient, as frequently happens, went to bed for the physician's visit. On rising afterwards the urine was free from albumen, and in the course of a little time became charged with it again, thus giving a double result in the twenty-four hours. With a patient of my own, in whose case I had always met with an absence of albumen in the early morning urine, I found upon one occasion the urine passed on rising contained a notable amount of albumen. The patient I discovered had been called upon to rise during the night for the action of the bowels, and had afterwards returned to bed.

The great point of interest in connection with the matter that is before us this evening is what information of practical value is supplied by the kind of proteid discoverable in the urine. Albumen and globulin are the principles that are found in association with the various forms of active renal disease, but they are also found when it cannot be considered that actual renal disease exists. By confining the attention too closely to the mere question of the chemical behaviour of the urine we are exposed to the risk of being misled. The case must be looked at in its entirety, not only looking broadly at the urine, but taking into consideration the points of *entourage* in connection with the patient, and when this is done it rarely happens that there need be any misgiving about the nature of the condition to be dealt with. We should look at the condition of the cardio-vascular system, look out for casts of tubules, and notice the amount of water passed. If you have urine high coloured, of good density, and with only a little albumen in it, that case stands in a very different position from one with a large quantity of pale limpid urine and with only a small quantity of albumen in it. Then when you go to look at the patient you can be in no doubt whatever as to the gravity of the condition of the patient before you. One frequently sees persons, because a little albumen has been discovered in the urine, put under very active measures of treatment, whereas I am sure that such would not have been the case, had the practitioner looked less at the condition of the urine and more at that of the patient.

T. G. Brodie.

Those of us who listened, at the last meeting of the Society, to Prof. Halliburton's most interesting paper when he opened his discussion will, I am sure, have been struck with one point upon which he dealt, namely, the relative proportion of the different proteids present in cases of albuminuria. The hypothesis he brought forward to explain why albumen is more constantly present than globulin is most interesting, and it is more particularly to this problem that I wish to direct your attention for a short time to-night. Prof. Halliburton's explanation depended upon the relative sizes of the two molecules concerned. Many experiments tend to show

most conclusively that in albumen we have to deal with a body that, chemically, may be regarded as less complex in character than a globulin; at any rate we have to deal with a proteid molecule of smaller size. The ordinary experience of filtration supports this view quite clearly. By simply filtering a strong proteid solution through filter paper we obtain a filtrate weaker in proteid than the original solution from which we started; and, as I have often experienced, this is much more likely to occur with a globulin solution than with an albumen solution. The experiments upon filtration through gelatin, using Martin's original form of experimentation, have also yielded me results which lead to the same conclusion. Since Martin first described his method I have carried out, for various purposes, many series of experiments in filtration, using gelatine solutions of very different strengths, and when filtering complex proteid solutions through these gelatine candles I have constantly found that should any proteid come through at all it is almost invariably albumen and not globulin if we are dealing with a mixture of those two bodies. I think it was quite clearly shown that the filtration in such a case depends simply upon the relative size of the molecules we are trying to filter with respect to the pores through which we attempt to press the substances. Thus, if we get a gelatine mass of sufficient density (one in which the gelatine molecules are packed sufficiently closely) we can stop the molecules in proportion to the minuteness of the mesh we form. It is quite easy to keep back .the complex proteid molecules such as albumen and globulin, and yet allow a simple molecule, such as albumose, to pass through. If we vary the strength of the gelatine, and, therefore, vary the closeness of the packing of the molecules of the filter, we correspondingly vary the power of the filter to keep back molecules of different sizes. One of the bodies among the coagulable proteids which it is difficult to keep back in such a method of filtration is hæmoglobin, and to the importance of this I wish to call your attention presently. If one obtain a more imperfect candle it is the albumen that comes through, the globulin being invariably kept back unless there be an actual flaw in the filtering medium. It is simply a question of density of the gelatine, and all these experiments, I think, tend simply to show that in albumen we have a molecule of smaller size than in the case of a globulin.

Now, with regard to the kidney, and the way in which albumen may appear in the urine. In some recent experiments upon which I have been engaged, I have been perfusing the excised kidney with defibrinated blood taken from the same animal, and I demonstrated this result to the Society at its meeting at the Examination Hall. In that case, and in fact in all our experiments, except at the very start, we were in reality dealing with a pathological kidney, not with a perfectly normal one, for albumen nearly always appears in the urine which is secreted. I use the term secreted because we can prove that it is in reality a true secretion, not a mere exudation or effusion, though sooner or later we always find some degree of albuminuria. The first proteid to appear in these cases is invariably hæmoglobin. The urine becomes tinted with hæmoglobin, and the amount of proteid present corresponds approximately to the amount of hæmoglobin present. Later in the course of the experiment, when the kidney is becoming more affected, we find more proteid coming through, and the fresh proteid which now makes its appearance is almost entirely albumen. There is a small quantity of globulin simultaneously present, but the amount is small in comparison with the amount of albumen. Still later in the experiment, perhaps some two hours later, blood begins to appear, and then we have reached practically the end of our experiment, for the kidney is becoming so affected, so many of its epithelial cells being changed, that our experiment must cease. As to the occurrence of hæmoglobin, that this appears dissolved in the urine is, I think, an indication that some has become dissolved in the plasma, and in confirmation of this we know that in the ordinary whipping of blood, the serum obtained is always tinted with hæmoglobin. Apparently the hæmoglobin can pass through the wall of a kidney tubule with relative ease. As soon as hæmoglobin becomes dissolved in the plasma it makes its appearance in the urine.

In another series of experiments I was dealing with a dead kidney. My experiments of filtration through gelatine led me to the idea that one could test the same method of filtration directly upon the kidney; that in the case of a kidney glomerulus it might be quite possible to employ it simply as a pressure filter, one comparable to a gelatine filter, but built up on a very minute scale; that if one could harden and fix the epithelial cells of the glomeruli, and subsequently pass through the vessels a proteid

solution, one might obtain a filtrate in the ureter. For this purpose I suddenly passed through the vessels of a kidney, immediately after its excision from the body, various hardening reagents, with the idea of rapidly fixing the capillaries and epithelial walls of the tubules, and keeping them in as intact a state as possible. The first hardening agent which I employed was warm methylated spirit. The injection was made suddenly under a fairly high pressure, so that all the blood was washed out before there had been time to precipitate it in the form of coagula which could block the capillaries. In this way I obtained a kidney which was practically free from blood. All the methylated spirit was subsequently washed out with water. I then transfused these kidneys with solutions containing different proteids, and found that I could obtain a filtrate, appearing through the ureters, which in the first instance contained, it is true, a little proteid, but only a little. Starting with serum or with egg-white diluted down to about one fifth of its normal strength, I obtained a filtrate from the ureters which contained proteid amounting to about one hundredth or one two hundredth of that originally present. In one or two favourable instances I obtained filtrates which were perfectly free from proteid, and contained only the salts of the transfusate. Now these experiments, I consider, lend very considerable support to the general view held as to the way in which the glomerulus works; blood passing through a kidney is exposed, when it reaches the glomeruli, to a certain pressure inside the capillaries, and the reason we get a filtrate which is free from proteid in normal urine, is simply and solely dependent on the size of the pores of the membrane through which the fluid has to pass. The imperfect results obtained in many of these experiments I think are of considerable value to us when considering the general question of albuminuria. In those cases in which I did not succeed completely, the proteid which appeared soonest was, in all instances, hæmoglobin. In my first experiments I was considerably disappointed, because I was always using a hæmoglobin solution. I thought it an advantageous one to employ, because the presence of hæmoglobin in the filtrate would show itself at once; but, without knowing it, I was applying the severest test of all to the kidney, and upon turning my attention to serum, instead of to

serum with blood-corpuscles dissolved in it, the results were more in accordance with the hypothesis I was testing. In those experiments in which the kidney obtained was imperfect, the proteid which more readily appeared was always albumen and not globulin; one had to obtain a relatively very imperfect filtration if the globulin was to appear in any quantity in the filtrate issuing from the ureter.

The results obtained by these experiments tend to support the explanation given as to the relative frequency of the appearance of the two chief blood-proteids in cases of albuminuria. Hæmoglobin will not appear in the urine unless hæmoglobin is dissolved in the blood-plasma, a condition of things which does not occur in ordinary cases of chronic Bright's disease. When the wall of the kidney tubule becomes partially impervious, then the proteid which has a small molecule passes through, *i. e.* the albumen rather than the globulin; and I think that the experiments I have briefly indicated to you to-night tend strongly to support this view, but they also have a bearing in another direction. The mere fact that the globulin is kept back whilst the albumen is allowed to pass through might, I think, indicate how far the kidney tubule is diseased. If this view be correct, the occurrence of albumen alone would indicate that we still have a practically complete membrane, though one in some way or other pervious to certain proteid molecules. Whether the membrane has become pervious because of a change in the epithelial cell, or because of a change in the cement substance between the cells, is a point which it would be extremely difficult to decide, though it is one which may be of very great importance. I think there can be no question that where the epithelial cells were actually shed, the proteids present would retain the relative proportions which they held in the blood. An intermediate condition would be a case where both these abnormalities were present, and would be indicated by the presence of both proteids, but albumen in a higher proportion than the globulin.

With this point in view, Dr. Russell kindly examined for me several albuminous urines from various cases. We found that in those cases where there was marked congestion, globulin was present in considerable quantities, and the ratios of the amounts of globulin and albumen were practically those known to occur

in the blood. This would indicate that the albuminuria was here a result of the imperfection of the tubule walls by actual loss of cells. In cases of chronic renal disease, of not too severe a type, a little globulin was detected, but most of the proteid was albumen. This indicates an imperfection in the tubules, but not an actual break in the continuity of the epithelial lining.

These are, briefly stated, the points I wished to bring forward this evening, and they chiefly deal with the physical conditions which may to a certain extent underlie the phenomena observed in albuminuria.

P. J. CAMMIDGE.

In carrying out some investigations on the albuminuria of Pregnancy and Eclampsia, which I recently undertook, I found it necessary to estimate the daily excretion of albumen and the relative proportions of the serum albumen and serum globulin passed in a number of such cases. In order to control these results I also examined the urine of some cases of ordinary nephritis uncomplicated by pregnancy.

Although the results obtained do not disclose any new or startling facts they are, I think, of some interest as, by the daily systematic examination of the urine which was made in each case, the relations between the proteid constituents of the urine in various forms of albuminuria are emphasised, and the operation of paracentesis, abortion, etc., on these relations shown.

The examination for proteids was always made on a specimen of the mixed excretion of twenty-four hours, and where pregnancy existed the urine was drawn off by catheter. The method employed for estimating the total proteid was that described by Devoto, namely, 100 c.c. of acid urine was filtered, saturated with finely powdered ammonium sulphate, and kept at 40° C. for several hours. It was then filtered through a filter-paper of known weight, and the separated precipitate washed with saturated ammonium sulphate solution. The filter and contained precipitate were dried, heated to 120° C. to coagulate the proteid, washed repeatedly with hot distilled water to remove the precipitated ammonium urate, excess of ammonium sulphate, and other soluble salts, and subsequently treated with alcohol and

ether and again dried at 40° C. They were then weighed, and after the ash present had been determined, the amount of proteid was calculated. To determine the quantity of serum globulin present Hammarsten's magnesium sulphate method was used. A specimen of the urine was made faintly alkaline with caustic soda, and after standing for some time the precipitated phosphates, etc., were filtered off. One hundred cubic centimetres of the clear filtrate were then saturated with powdered magnesium sulphate and kept at 40° C. for several hours. The precipitate was collected on a weighed filter and washed with saturated magnesium sulphate solution until the washings no longer gave a proteid reaction. It was then dried and heated to 110° C., repeatedly washed with hot distilled water, alcohol, and ether, again dried and then weighed. The ash was determined and the amount of serum globulin calculated. The difference between the results obtained by these two methods was taken to represent the serum albumen in 100 c.c. of the urine.

Although these processes are not perfect, they give fairly accurate results, especially when, after a preliminary examination of the urine, attention is devoted to minimising the known sources of error. They were, too, the most suitable for using on the large scale necessary for my purpose. And where, as in the present instance, large numbers of observations made under similar conditions were compared together, absolute accuracy was not a matter of such prime importance.

The actual weighing in each case was carried out to three places of decimals, but the experimental error was too great to admit of the final result being stated to more than one place at most. Albumoses were sought for in the preliminary examination of the urine in most cases. They were, however, only rarely met with, and then only in very small quantities.

In the charts of the nine cases, which I have selected as fairly typical of different classes of albuminuria examined, the total proteid in grammes per litre and the total proteid in grammes are shown in the upper division, the former by a dotted line, and the latter by a continuous line. In the lower division the serum albumen is represented by a continuous line, and the serum globulin by a broken line, both being stated in grammes per litre. The presence of casts in the urine is indicated by crosses at the head of the columns.

Case 1. *Acute nephritis.*—Thomas C—, aged 30 years. Under observation from November 4th to November 14th, 1898.

Past history.—An iron-moulder. For the last three years had earned his living as a hawker. No history of scarlet fever, etc.; no previous attacks.

History of present condition.—Three weeks ago got very wet and caught a severe cold, but continued his work. Two weeks ago pain in the loins, legs swelled, urine dark coloured and diminished in quantity. One week ago face and eyelids puffy.

Present condition.—Anæmic, face puffy, chest-wall œdematous, legs and genitals œdematous, but no ascites. Heart-sounds clear; first sound accentuated. Cardiac dulness appears normal. Pulse rather high tension; arteries somewhat harder than normal. Complains of severe headache and vomiting. Urine, sp. gr. 1007—1018; urea, 2·7—1·1 per cent.; granular casts, some blood; albumen, 3·4—1·2 grammes per litre.

Death on November 15th.

Post-mortem.—Large mottled (spotted) kidney; microscopically, parenchymatous nephritis with some glomerular change.

Total duration of disease about five weeks.

Case 2. *Acute nephritis.*—Alfred N—, aged 6 years. Under observation January 18th to March 3rd, 1899.

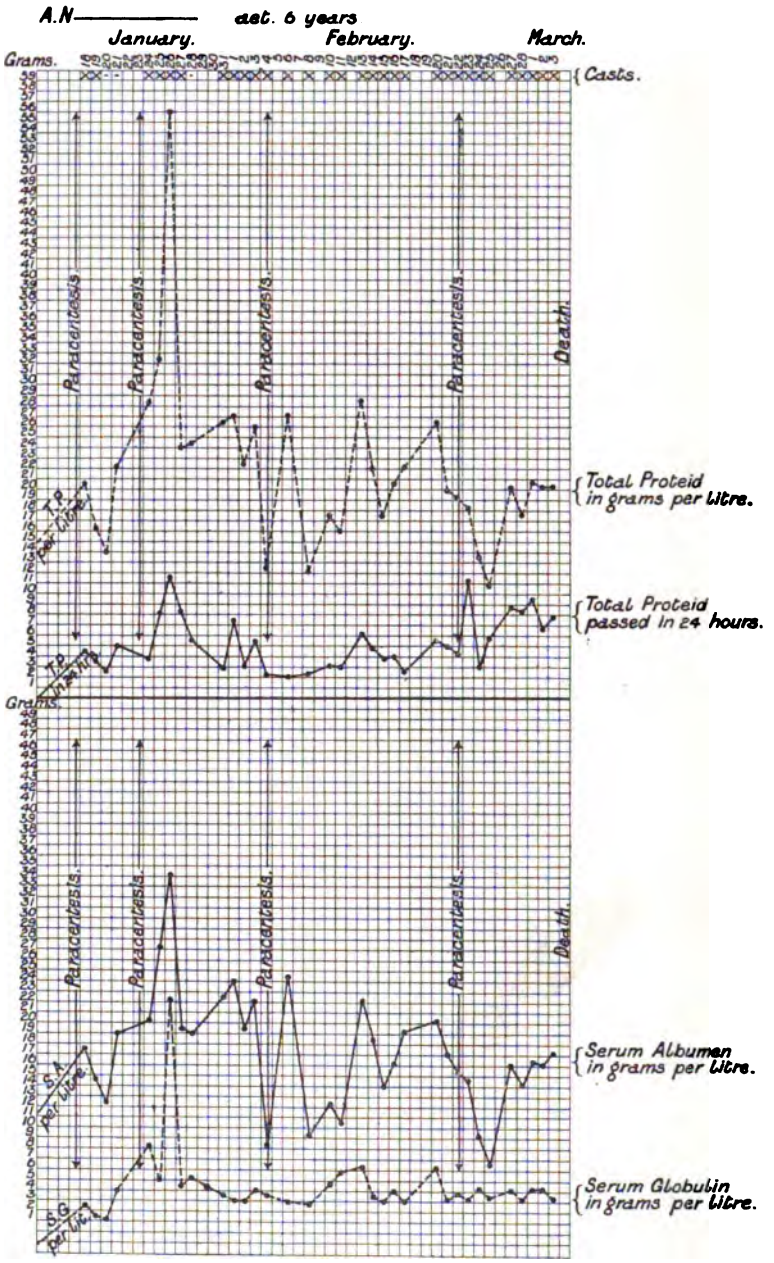
Past history.—Three years ago had measles, chicken pox, and whooping-cough; October, 1898, bronchitis.

Family history.—Two great grandmothers, grandmother, and two aunts, all on his mother's side, died of "dropsy and Bright's disease."

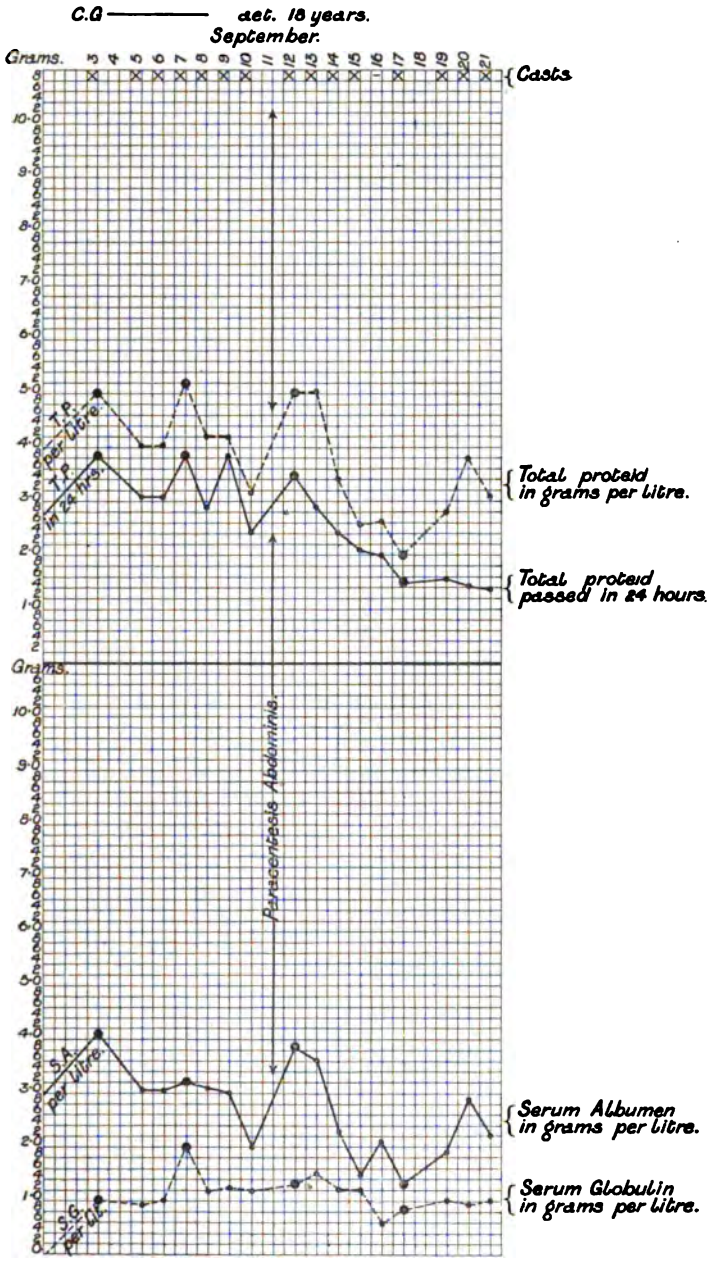
History of present condition.—December 4th, 1898, face swollen; December 8th, feet and legs swelled; January 4th, 1899, suppression of urine for twenty-four hours.

Present condition.—Very anæmic; face puffy; legs œdematous; much fluid in abdomen, which when withdrawn by Southey's tube (five and a half pints) on January 17th showed total proteid, 2·20 grammes per litre; serum albumen, 1·50 grammes per litre; serum globulin, 0·70 gramme per litre. Lungs œdematous at both bases. Cardiac dulness a little enlarged; no murmurs. Urine, sp. gr. 1024—1035; urea, 2·2—4·5 per cent.; hyaline and granular casts, some blood; albumen, 56·3—11·0 grammes per litre.

CASE 2.—Acute Nephritis.



CASE 3.—Chronic Parenchymatous Nephritis.



Death on March 4th.

Post-mortem.—Large white kidney; microscopically, parenchymatous nephritis.

Total duration of disease from four to five months.

Case 3. *Chronic parenchymatous nephritis.*—Charles G—, aged 18 years. Under observation September 3rd to 21st, 1898.

Past history.—A gas-fitter. Scarlet fever when a child.

History of present condition.—March, 1898, legs swelled and he gave up work. April, abdomen swollen. May, face swollen in morning; pain in loins, headache, nausea.

Present condition.—Anæmic; thoracic and abdominal walls œdematous; some ascites; legs pit on pressure. Heart: slight diastolic murmur at aortic base. Pulse 96; arteries rather hard. Urine: sp. gr. 1018—1012; urea 2·7—1·3 per cent; hyaline and granular casts, no blood; albumen 5·2—2·0 grammes per litre.

September 11th, paracentesis abdominis, six pints. Total proteid, 2·6 grammes per litre; serum albumen, 1·7; serum globulin, 0·9.

Case 4. *Chronic parenchymatous nephritis.*—Edward J—, aged 30 years. Under observation August 20th to September 9th, 1898.

Past history.—Shop assistant. Three years ago pain in loins and some swelling of feet, which quickly subsided under treatment. One year ago similar attack, but lasted longer.

History of present condition.—May, 1898, pain in the back; severe headache, with some nausea; legs and abdomen swollen.

Present condition.—Anæmic; face rather puffy; legs swollen; some ascites. Heart natural. Pulse 76, soft and regular. Urine: sp. gr. 1005—1016; urea 0·8—2·1 per cent; hyaline and granular casts, no blood; albumen 11·0—1·5 gramme per litre.

Case 5. *Hip-joint disease; amyloid kidney.*—James P—, aged 9 years. Under observation September 20th to October 11th, 1898

Past history.—Measles, whooping-cough, but not scarlet fever. When five years of age he was treated for hip disease in the Alexander Hospital for two years.

Present condition.—Hip-joint disease on left side with several discharging sinuses. Face pale and waxy. Liver considerably enlarged. Heart: marked reduplication of second sound at pulmonary base, with short systolic murmur. Slight general œdema. Urine: sp. gr. 1005—1012; urea 0·3—0·9 per cent.; pus and hyaline casts, no blood; albumen 7·3—3·0 grammes per litre. The filtered urine still contained a considerable amount of nucleo-proteid and traces of albumose.

Case 6. *Albuminuria of pregnancy.*—Mary C—, aged 25 years. Under observation November 7th to December 17th, 1898.

Past history.—Chorea as a child. No albumen in the urine before pregnancy.

Present condition.—First pregnancy, seventh month. Some œdema of legs and vulva. Dull, apathetic, and constant violent headache. Urine: sp. gr. 1008—1027; urea 0·5—2·4 per cent.; granular and hyaline casts; no blood; albumen 0·2—2·7 grammes per litre.

Premature labour induced November 14th, 1898; fœtus born dead.

November 12th to 18th, diarrhœa.

Case 7. *Albuminuria of pregnancy.*—Sarah C—, aged 21 years. Under observation November 18th to November 30th, 1898.

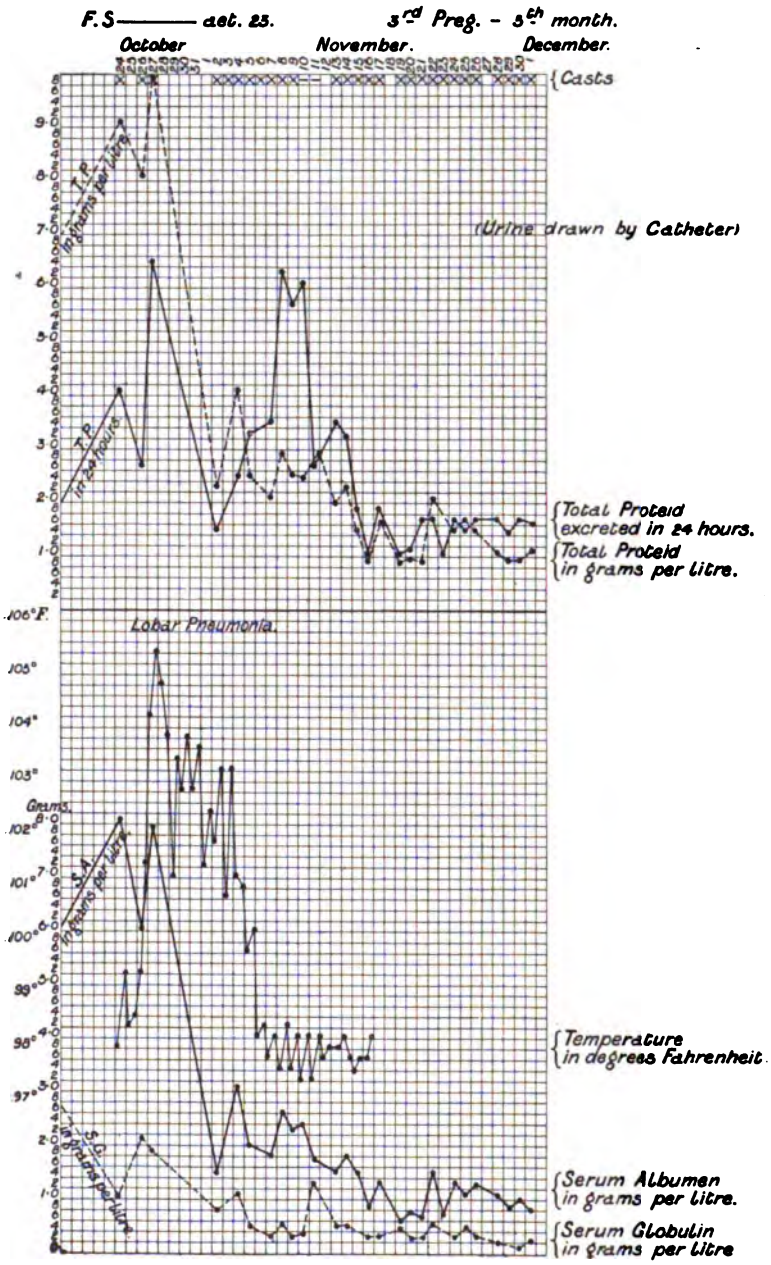
Past history.—Bilious headaches since a child. Pregnancies two; one miscarriage (fifth month); one labour (seventh month); child stillborn on May 25th, 1898.

Present condition.—Third pregnancy, fourth month. Severe headache and constant vomiting; no œdema. Heart: second sound accentuated. Urine: sp. gr. 1010—1019; urea 0·7—2·3 per cent.; hyaline, granular, and some blood-casts; albumen 0·5—14·5 grammes per litre.

Premature labour induced November 25th, 1898; child born dead.

Case 8. *Albuminuria of pregnancy.*—Florence S—, aged 23 years. Under observation October 24th to December 1st, 1898.

CASE 8.—Albuminuria of Pregnancy.



Past history.—Two children, last November, 1897; no scarlet fever, measles, etc.

Present condition.—Third pregnancy, fifth month. Pale and anæmic, puffy under the eyes, legs swollen, some œdema over sacrum. Heart: local apical systolic murmur. Urine: sp. gr. 1006—1018; urea 0·7—2·4 per cent.; hyaline, granular, and blood-casts; uric-acid crystals frequently present; albumen 0·8—9·8 grammes per litre.

October 27th.—Rise of temperature to 105·6° F., with cough and signs of pneumonia in left lung.

November 11th.—Both discs blurred, and some blurring of vessels in right eye.

January 10th, 1899.—Child born alive.

Case 9. *Eclampsia.*—Jessie M—, aged 17 years. Under observation May 23rd (first examination of urine May 25th) to June 1st, 1899.

Past history.—No scarlet fever; measles when a child.

History of present condition.—May 17th, face puffy, feet swollen; urine dark colour.

Present condition.—Not anæmic, face puffy, feet and vulva rather œdematous, severe headache, apathetic, some vomiting.

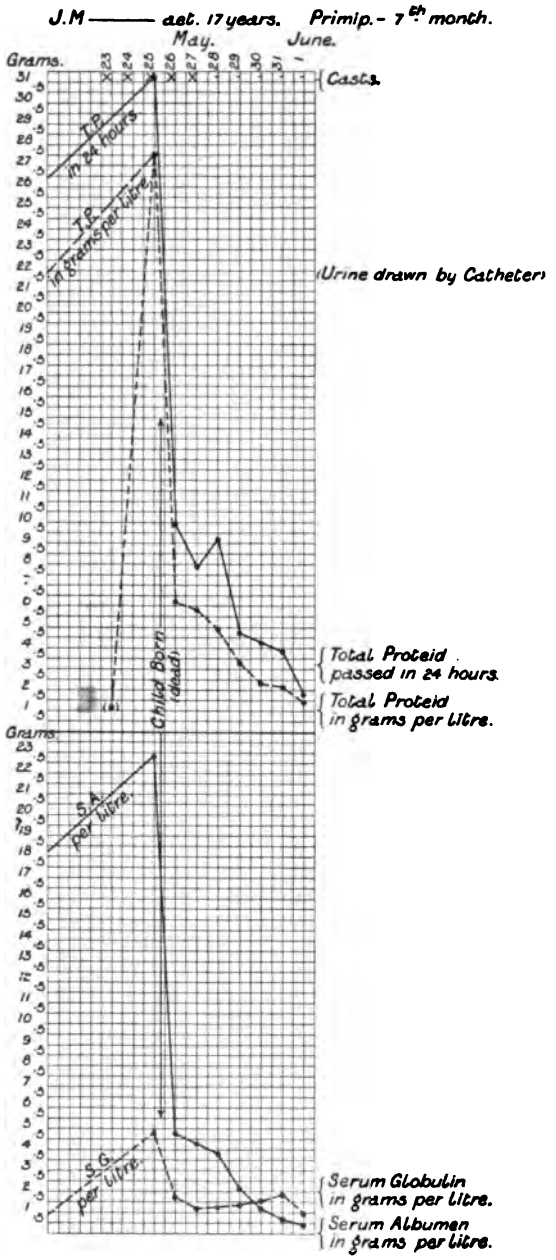
May 24th.—Had twelve violent convulsive attacks in the twenty-four hours.

May 25th.—Premature labour induced, child born dead; convulsions ceased. Urine: sp. gr. 1010—1036; urea 3·2—0·3 per cent.; granular, hyaline, and some epithelial casts; methæmoglobin; albumen 27·6—1·4 grammes per litre.

On comparing the charts, given by daily observations of the albumen excretion in the various forms of albuminuria illustrated above, certain relationships are at once evident, whilst others are only suggested, and require confirmation by wider experience with a larger number of cases.

Considering first the total proteid, the curves representing the total proteid in grammes per litre and the total proteid passed in twenty-four hours, correspond fairly well, as a rule, except in the two fatal cases of acute nephritis (Cases 1 and 2), where several marked variations in the latter a few days before death are unrepresented, or only feebly shown, in the former. In

CASE 9.—Eclampsia.



Case 3, a case of chronic nephritis, the total proteid in twenty-four hours diminished steadily as the patient improved, but the total proteid in grammes per litre still showed marked oscillations. Where albuminuria was associated with pregnancy the fall in the excretion of proteid which followed labour was less sudden, but generally in the end more marked in the total proteid calculated on the day's excretion than when reckoned in percentages.

After paracentesis a similar state of things was usually found. In Case 7, where pneumonia supervened as a complication of the albuminuria of pregnancy, the total proteid in the twenty-four hours' curve showed a very marked rise after the crisis, whereas the other was scarcely affected at all. The total amount of proteid material lost in the day in the urine depends, of course, not only on the percentage of proteid present, but also upon the amount of urine excreted, and it is owing to the variations in the quantity of water passed that the two curves do not correspond. Many clinicians are content merely to observe the amount of albumen present in a sample of urine, but my experience tends to show that this cannot be taken as a safe indication of the severity of the disease, and that it is necessary to estimate the total quantity passed in twenty-four hours to obtain a reliable guide.

Turning next to the excretion of serum albumen and serum globulin, it is found that the amount of serum albumen is nearly always considerably greater than the amount of serum globulin, in fact I have rarely met with instances where the globulin was in excess, even in eclampsia. In only one of the five cases of eclampsia in which I have had the opportunity of examining the urine with care did I find the serum globulin to exceed the serum albumen in amount, and then only for three days, commencing on the fifth day after delivery (Case 9). In Case 5. albuminuria of pregnancy, the globulin was slightly the greater (s. g. 0·6 gramme per litre and s. a. 0·4 gramme per litre) on the eighth day after delivery. In these two cases it will be noticed that, although the effect of delivery was to cause a drop in both curves, the serum albumen was more markedly affected in each case by that event, and in a few days had fallen so low that the more persistently high excretion of globulin was the greater of the two, but in neither patient did this relationship last for long. That delivery does not always produce this effect is shown in Case 7, where abortion was followed by a simultaneous

rise in both globulin and albumen excretion, which was, however, less marked and of later date in the globulin. In the case of hip-joint disease (Case 5) they were equal on two occasions, and throughout the period during which this case was examined the difference was less marked than in any other. This may be explained by the fact that, although the urine was filtered from the pus which it contained when passed, a considerable amount of nucleo-proteid was found to be dissolved in the filtrate, and as this would be precipitated with the globulin and other proteids and remain unaffected by the subsequent operations in the precipitate, the relative proportion of serum globulin would appear higher than it should be. It is possible that conversely a somewhat similar explanation of the rarity with which an excess of globulin was met with in the cases of eclampsia I examined may be given. The invariable use of the catheter in all my cases where pregnancy was present would avoid admixture of mucin (nucleo-proteid), derived from the genital tract, with the urine, and so prevent an unusually high value being given to the globulin reading. In the two fatal cases of nephritis (1 and 2) the serum albumen was always much in excess of the serum globulin, and in neither curve can any very marked variation be taken as foreshadowing a fatal termination in either case.

In the charts which I have given it will be seen that the most marked variations occur in the excretion of serum albumen, the serum globulin remaining at a more constant level, and this I have found to be true in all the cases I have examined. A larger proportion of serum globulin is, however, generally found in the more severe cases, and where during life the amount passed in the urine is great, the kidneys, when examined microscopically *post mortem*, are found to have undergone more profound and wide-spread changes. The more marked the variations in the quantity of serum globulin excreted, the more severe, as a rule, is the case. The serum albumen is not as good an indicator as the serum globulin of the extent of the damage suffered by the kidneys. It is subject to very wide variations, and a marked rise may often follow slight exertion or a little change in the diet; rise of temperature, too, is generally accompanied by an alteration in the amount of serum albumen excreted. Owing to the greater constancy of the serum globulin curve, the serum

albumen output is generally found to vary with the total proteid excretion.

I have already referred to the effect of premature labour on these two curves, and it now remains to be seen how paracentesis affects them. The result is usually comparable with that produced by labour, for while the serum globulin is only very slightly or not at all affected, the excretion of serum albumen is considerably influenced. Generally it is increased for the next two or three days, but occasionally it falls, as it usually does after the fœtus has been expelled, in the albuminuria of pregnancy. As the fluid re-accumulates in the abdominal cavity a return to approximately the former level takes place.

The subject of nephritis and albuminuria covers such a wide field, that any investigation, such as I have undertaken, can but touch a very small portion of it. I think, however, that my researches have suggested some points which only require more extended observations to demonstrate with greater clearness, and which, even now, may prove useful in clinical medicine.

1. The percentage of albumen present in a specimen of the urine cannot be taken as a safe guide in estimating the severity of the disease, but the total quantity passed in the twenty-four hours is a more sure indication.

2. A large proportion of serum globulin is usually found in those cases where the kidney is seriously affected.

3. The excretion of serum albumen is more variable than the excretion of serum globulin, and is more easily influenced by extraneous circumstances.

4. The amount of serum globulin rarely exceeds the amount of serum albumen, even in eclampsia, and is generally much less.

GOWLAND HOPKINS

said that in a case of physiological albuminuria which he had examined in a man, aged 21, who was in perfect health, the condition was closely related to diet, the amount of albumen being greatest about four to five hours after a meal. Examination at various times showed that the proteid was not always the same; for instance, on a diet of bread and milk only it was found that the proteid contained no loosely-combined sulphur, whereas on an ordinary diet this was always present. He thought

that this difference of result depended on the synthesis of the different proteids in the intestinal canal, and not on the kidney.

LEE DICKINSON.

Most of what I have to say is rather clinical than pathological, which perhaps is one way of saying that it is rather vague. I can only touch upon one branch of the subject, that is the presence in the urine of peptones and albumoses. First, as regards the presence in the urine of Kühne's hetero-albumose or Bence Jones's albumen. It seems that the exact name does not matter very much, nor do the precise chemical actions, because it is evident that there is a group of bodies which are very similar one to another, some of them being more like albumose and others more like albumen. As an example of the latter I might mention the substance which Dr. Hutchison described at the last meeting in a case of bone disease, which he said was a true albumen, not an albumose. But the main point seems to me to be that all these substances are distinguished from ordinary proteids by the fact that they coagulate on the application of heat at a very low temperature, and the coagulum is re-soluble at a somewhat higher temperature. This group of substances is, as is well known, almost always associated with disease of bones, either osteomalacia, or myeloid sarcoma of the bones of the trunk chiefly; but what I want to point out is that it is not only in bone disease that this kind of substance is found, but also in some other diseases. For instance, it has been discovered in glycosuria—I do not know whether in true diabetes, but at any rate in association with sugar in the urine. Dr. Fitz, a well-known American physician, found it in a case of fatal myxœdema. I believe a *post-mortem* examination was not made, but there was no reason to suppose that the bones were diseased, and all that Dr. Fitz could find out was myxœdema, and the presence of hetero-albumose in the urine. Also it has been found in leucocythæmia. I think there are some published cases of this kind, though I do not know where they appear; but I know of one case, which occurred in the practice of Mr. Edgcombe Venning, in which there was no reason to suppose that the patient suffered from anything but leucocythæmia of the ordinary kind.

There is one important clinical point about this kind of albumosuria, and that is that it is always of fatal omen. I believe that whenever this substance has been discovered in the urine, death has occurred within at most a very limited number of months, whether the case was one of disease of bone marrow, or of the other kinds to which I have referred.

Secondly, as to the more ordinary kinds of albumosuria, what Professor Halliburton tells us ought more properly to be called peptonuria, that is to say the presence of proto- or deutero-albumose in the urine; this has been described in a wide variety of conditions, amongst others measles, scarlet fever, typhoid fever, scurvy, the puerperal state, rheumatism, and cerebro-spinal meningitis. I doubt if peptones or albumoses are really present in the urine in all these conditions, because most of these observations were made several years ago, since which time physiological chemistry has advanced. Certainly the chemical differences between some of the nucleo-proteids and albumoses are rather small, and confusion might easily arise in dealing with very small quantities. With regard to cerebro-spinal meningitis, I think there is less doubt admissible, for, as Professor Halliburton has shown, even the normal cerebro-spinal fluid contains albumoses, and one can easily believe that when this fluid is largely increased in inflammation of the membranes, the albumoses are absorbed into the blood and excreted in the urine. In one class of cases peptonuria or albumosuria does occur very obviously, I mean cases where suppuration is present, or at any rate, extensive inflammatory exudation, and more particularly I would say cases of inflammatory chest disease in the acute stages, such as pneumonia and empyema in the pleura. Some years ago Dr. Fyffe, of Wellington, and I examined a large number of cases of medical disease to be found in the wards of a general hospital, with reference to the presence of peptones in the urine, and found it to be almost limited to the cases of pneumonia and empyema. At that time influenza was particularly rife, and although all our cases were not influenzal, still the type of chest disease was unusually severe, and we found peptonuria in a far greater proportion of cases than one is likely to find it at the present time. In one case, where empyema was developing, the urine contained at least 1 per cent. of proto-albumose, and that at a time when the urine was not scanty in quantity, but was rather more

abundant than natural. That, I need hardly say, meant that while this substance was passing through the blood a great toxic influence must have been exerted upon the patient; indeed, he was profoundly ill. He did not die at the time, but he died not long afterwards from bronchiectasis resulting from this illness. Our failure to find peptonuria in many diseases where we sought for it, may have been due to the fact that we only concerned ourselves with those quantities which can be demonstrated readily and quickly at the bedside. Our methods were to test for it with nitric acid, and with the biuret test, which is a very useful preliminary, though not particularly reliable by itself. In the application of nitric acid a little care is necessary to obtain the right proportion; and it is well to first remove the ordinary albumen which is invariably present, though sometimes only in traces. Of course the characteristic reaction is the disappearance of the nitric acid precipitate on warming, and its reappearance on cooling. Now as to the clinical significance of this peptonuria; it cannot be relied upon as a sign of empyema because it occurs almost as frequently, though perhaps not in such large quantities, in pneumonia, where there is no suppuration. I have also seen it in fibrinous pleurisy, where there is not even pneumonia, and on two occasions in purulent bronchitis.

The phenomenon is associated with severe illness, and probably means that the infecting organism—pneumococcus, streptococcus, or whatever it may be—has met with little resistance on the part of the patient, and has not only produced its characteristic lesions in the shape of pneumonia, empyema, or the like, but has carried its activity further to the production of the toxins and proteolytic bodies in question at the seat of the disease, which are then excreted in the urine.

Nevertheless, given a bad case of pneumonia or empyema with symptoms of toxin poisoning, one would rather see peptonuria than not, for its presence shows at least that the kidneys are capable of excretion. I use the term "excretion" advisedly, because I think these albumoses are actively excreted by the kidneys and not merely diffused out; for although they diffuse better than albumen, they do so far less well than true peptone. In some of the worst cases, where the general symptoms are even more severe than the local, peptonuria is absent throughout.

In conclusion, I will only remark that peptonuria is not often

met with in abdominal affections, whether visceral or peritoneal. The explanation is probably afforded by the comparative chronicity of abscesses and inflammatory exudations in the abdomen, and by the fact that these are apt to be surrounded by a thick membrane which impedes absorption; whereas the lung or a virgin pleura, when they become the seat of acute disease, present ideal facilities for rapid absorption. However, when an abscess ruptures suddenly into the peritoneal cavity, peptonuria to a marked degree may result, and under these circumstances is a matter of some value in diagnosis.

A. E. Garrod.

It seems to me that in considering the causation and clinical significance of albuminuria we must not leave out of consideration the fact that, although healthy kidneys do not under normal conditions allow albuminous substances to pass into the urine, under certain circumstances kidneys which are apparently healthy excrete even such proteids readily. I may quote the example of paroxysmal hæmoglobinuria, in which disease hæmoglobin appears in large quantities in the urine during the attacks, although both before and after the paroxysm the renal excretion is usually proteid free. Dr. Brodie's observations are of great interest in this connection. One has been in the habit of regarding this phenomenon as an example of the readiness with which a proteid which is not a normal constituent of the blood-plasma is got rid of by the kidneys, but his results with perfused kidneys and with Martin's filter suggest the possibility that the kidneys, although normally impervious to serum albumen and globulin, may, for purely physical reasons, be pervious to hæmoglobin. We know, at least, that when free hæmoglobin is present in the plasma in more than a small amount it quickly appears in the urine.

However there is other evidence that foreign proteids are not retained by healthy kidneys, and I may quote as an example the experiment of the injection of egg albumen into the circulation of animals. Even when egg albumen is taken largely by the mouth, in a raw state, albuminuria results, as Mr. D'Arcy Power has shown.

If, then, it be a fact that the kidneys are permeable by a pro-

teid which is, so to speak, foreign to the blood, is it not possible that in some cases of so-called physiological albuminuria the fault may reside in the proteid rather than in the organism which excretes it? We know of examples of abnormal metabolism which are congenital and persist through life, such as alkaptonuria and cystinuria, and it is not improbable that minor and less obvious anomalies of the chemical processes within the body are not very uncommon (I am aware that the anomalies quoted have been ascribed to bacterial infection, but many obvious difficulties are presented by such a theory). It therefore seems possible that just as the hæmoglobin of one animal differs from that of another, as is shown by differences of crystalline form, so even in the human body slight abnormalities of metabolism may lead to the presence in the blood of proteids deviating somewhat from the normal type, which may be excreted by the kidneys. This is, of course, a pure hypothesis, which can only be tested by a careful examination of the proteids occurring in the urine in such cases, and the observation which Mr. Hopkins has recorded this evening suggests that investigations directed to this point may not prove wholly fruitless.

F. Parkes Weber.

I should like to allude to a point which I believe to be of some practical importance. This is the probable significance of what is generally termed a "very faint trace of albumen" in the urine. I refer to urines (generally of extremely low[1] specific gravity) in which some of the ordinary clinical tests for albumen give a faint but distinctly positive result; I am not here taking into consideration the delicate tests (with concentration of the urine, etc.) by which a trace of albumen or nucleo-proteid has been found in almost every urine. When a urine is clear and remains just as clear on the gradual addition of acetic acid in the cold (to exclude the presence of

[1] I have especially noticed this reaction when the urinometer sinks down to zero (or nearly so) in the urine when freshly passed. On cooling, the specific gravity is of course slightly higher. Hurry, excitement, chilly weather, and (especially) alcoholic drinks, may all lead to the passage of such a urine, especially in the case of excitable individuals and neurasthenics; in these persons a draught of some mineral waters may act in the same way.

"mucin"), and when, on testing another portion of the same sample, the upper part of the test-tube column remains clear after boiling, and the addition of a few drops of acetic acid produces a slight opacity in the boiled part, this urine is commonly said to contain a "faint trace of albumen."

My own opinion is that in such urines the faint opacity produced by adding acetic acid after boiling may be due not to the presence of albumen but to the presence of "mucin." I find that when a watery fluid containing lumps of clear glairy mucus (derived from any mucous membrane) is tested by the above-mentioned method, the addition of acetic acid in the cold (of course) produces an opacity, but the opacity is decidedly greater when the fluid has been boiled just previously to the addition of the acid. It is, therefore, very probable that the presence of a small amount of "mucin" in the urine, though not sufficient to give rise to an obvious opacity on the addition of acetic acid in the cold, may yet cause a faint but distinct cloudiness when the urine has been boiled before the addition of the acid.

Although perhaps at first sight the point I allude to may be considered a trivial one, it is, I believe, in reality one of considerable practical importance. In questions of life assurance, for instance, there is naturally a very great prejudice against the lives of persons (especially if over thirty years of age) in whose urines the medical examiner reports the presence of a trace of albumen. Is one justified in stating *positively* that the urine does really contain a trace of albumen when it merely gives the reaction (and in the slightest degree only) to which I have alluded? I am myself by no means convinced, and I should like to hear some opinions on the subject.

Moreover, if the reaction in question be regarded as often due to the presence of "mucin" without albumen, I think the frequency of cases of so-called "albuminuria in apparently healthy subjects" must be somewhat reduced. I do not wish by any means, however, to call in question what everyone must recognise as a fact, viz. that a moderate degree of albuminuria is by no means rarely found in apparently healthy persons. On this subject, however, about which so much has been said of late, I have no intention of entering at present.

There is one other point to which I wish to refer. I have had the opportunity of examining bilious urines from various cases of

intense chronic icterus due to malignant disease (or grave cholelithiasis) with obstruction of the common bile-duct. The urines I now speak of presented the following reaction, which has, I believe, frequently been noted by medical observers in *grave* chronic cases of deep icterus. When a little acetic acid is added in the cold (the urine having been previously filtered, if necessary) a cloudiness appears, which gradually disappears when excess of acetic acid (about half and half) is added, though sometimes it is necessary to heat the urine with the excess of acetic acid before the precipitate quite re-dissolves. The presence of a little albumen (as in a specimen of bilious urine which I have brought with me this evening) does not disturb the reaction, for by the addition of acetic acid in the cold the albumen becomes changed into acid albumen, and is therefore not precipitated by the subsequent heating. The reaction in question has been attributed to various causes, but I suppose that it is due to the presence in the urine of the so-called "bile-mucin," which after being absorbed by the blood from the obstructed bile-passages, is then, together with the bile-pigments and bile-salts, excreted by the kidneys. According to Professor Halliburton ('Chemical Physiology and Pathology,' 1891, p. 679) "bile-mucin," the slimy substance in the bile,[1] is a mucinoid material (chiefly a nucleo-albumen) which can be precipitated from bile by means of acetic acid or by excess of alcohol, but which, unlike true mucin, is slightly soluble in excess of acetic acid. The presence of this mucinoid substance (whatever its exact nature may be) in the urine is, I believe, generally associated with the presence of a considerable number of tube-casts containing dark brown pigment granules. Some of the casts contain small cells loaded with brown pigment. I believe that some of these pigment-bearing cells are a kind of scavenger cells, which after collecting bile-pigment and *débris* from decaying hepatic cells, and after finding their way into the general blood-stream, are then got rid of with the urine. Similar cells probably lodge in the skin, and by breaking up and depositing their pigment there give rise to the intense blackish pigmentation of the

[1] I do not here refer to the true mucus secreted in the gall-bladder, but to a substance found in the bile in the hepatic ducts, which are said to secrete no true mucus. In some cases of biliary obstruction, a slimy mucinoid substance may be present in excess in the secretion found after death in the hepatic ducts.

skin seen in certain cases of very chronic icterus. It seems to me that such scavenger cells, by carrying the *débris* of hepatic cells to the kidneys, may possibly account for some of the "bile-mucin" in the urine of these cases; I do not think that the mucinoid substance in question is derived either from the mucous membrane of the gall-bladder or from any part of the urinary passages.

The cases, I believe, in which this reaction is well marked are all grave cases. I would ask if the substance spoken of in an epitome paragraph entitled "A Source of Error in testing for Albumen in Icteric Urine" ('Brit. Med. Journ.,' August 22nd, 1891, Epitome No. 193) is not really "bile-mucin," though in the notice in question it is considered to be bile-acid or bile-pigment.

W. P. Herringham.

We should expect that in albuminuria the varying amounts of the two chief urinary proteids would be of clinical and pathological importance; and the first attempts at analysis (Senator's and Maguire's) to some extent bore out this hope.

But since the discovery of the fractional separation of albumen and globulin by magnesium sulphate (Hammarsten), or ammonium sulphate (Pohl), has rendered the analysis more trustworthy, the experiments made in Edinburgh (Noel Paton with pupils, and Boyd) have overthrown these results. They have proved that the variation of the proteid quotient is, on the one hand, so great that it cannot be determined by any variation in the blood, and on the other, so irregular that it cannot depend upon any structural alteration in the kidney. It varies from a small decimal to infinity, and in the same patient it varies at different times in the day.

It seems at first sight to be deprived of all significance, and, indeed, of diagnostic significance it is actually at present deprived.

Nevertheless this conclusion must be to some extent discounted. In the first place, the present classification of renal disease is far from final, and it is possible that when we reach a stage of lesser ignorance the proteid quotient may be of more importance than it is now. In the second place, what may be called the physio-

logical or natural variation of a pathological condition which Noel Paton described, should, if found to be constant, throw light upon the function of the kidney. If his figures are examined it appears :

1. That the urine of night contains the smallest percentage of albumen, and that passed soon after breakfast the largest. From 10 a.m. the percentage falls—not always evenly—through the day.

2. Serum globulin shows no such variation.

3. A diet poor in nitrogen lessens the albumen, but has little effect on the globulin.

4. A milk diet diminishes the albumen, but diminishes the globulin still more.

The two factors do not vary together, so that to talk of the proteid quotient, and to lay stress upon it, distracts the attention from the variation in albumen, which is the remarkable and important thing.

The percentage of albumen, and not the actual amount passed, is the more important. The latter depends only upon the urinary water.

Thus the beginning of the day's digestion after the night's rest, which we know produces a large excretion of salts, and which in some persons produces what is called functional albuminuria, leads in these cases of chronic Bright's disease to an unusual excretion of serum albumen, though the globulin is unaffected.

Lastly, to return to the first point of the two, it is to be remembered that the pathology of Bright's disease has not advanced for thirty years, and is in great confusion. The plain fact is that while clinical and pathological investigations have become much more laborious and minute in other departments, they have not improved in this. We are still content to note the amount of albumen and of urea, although we know that neither the one nor the other gives a reliable clue to the expectation of life. We are still content to say that a kidney is affected with parenchymatous or interstitial nephritis, although we can thereby give no explanation of the death. This last depends upon conditions of the heart or nervous system, for which as yet we can offer no account, and it appears probable that until clinical investigation pushes chemical analysis of the urine farther, and until patho-

logists take regular account of the permutations and combinations of individual morbid lesions, we are not likely to know much more of Bright's disease than the generation before us.

W. D. HALLIBURTON, F.R.S.,

In reply, said: I shall not detain you very long in adding a few closing words to this lengthy debate. First, I thank you, Sir, for the kind way in which you introduced me, a visitor, to the members of the Society, and although I am afraid I was not able myself to bring forward anything in the way of new knowledge, yet I think, if I may venture to say so, that this discussion has brought together a large mass of different material, which has illuminated very many branches of the very wide subject which is covered by the name albuminuria. We have had records of rare, and in some instances mysterious cases; we have had from Dr. Bradshaw and Dr. Hutchison complete accounts of the condition associated with softening of bones. We have had from a physiologist a very suitable case of physiological albuminuria, and that, too, a suggestive one. We have also had papers that have presented the subject in a more general way, both from the laboratory and bedside point of view. We were fortunate enough to secure the contribution of Dr. Pavy, who has both kinds of experience; and although Dr. Pavy slightly misunderstood one or two remarks that I made about sugar in the urine, I did not think it worth while to interrupt him at the time, because it would have put a stop to that vivacious flow of language and that enthusiasm which is always so admirable in all that Dr. Pavy has to say.

With regard to Dr. Brodie's experiments I would only point out how very forcibly they confirm the ideas that I ventured to put before you. Perhaps that is not quite the correct way of stating the real fact; it is rather putting the cart before the horse. It was not until I knew of Dr. Brodie's experiments that I ventured to put forward in somewhat more positive terms than I might otherwise have done, the theory about the size of molecules and permeability of cells that I laid before you. It seems to me a very striking proof of the physical side, as opposed to the vital side, of physiological explanations that Dr. Brodie has

got a kidney which he has kept six months in formalin, and is able to make it produce urine. That seems rather a spoke in the wheel of those who are fond of putting forward the word "vital" as one that explains everything, although it really explains nothing.

One or two words with regard to Mr. Cammidge's remarks. I should be sorry to say anything unkind after having listened to his interesting paper, especially as he himself disarmed criticism by saying that his methods were rough. He admits the presence of pus, and the possibility of an upset to his calculations that this might have caused. Dr. Lee Dickinson mentioned another source of error in the presence of albumose in many cases of eclampsia, and that does not seem to have been taken into account in the analyses that were presented to us. No doubt for clinical purposes—that is the lofty way in which laboratory people sometimes speak about clinical observations—for clinical purposes the methods used are sufficiently accurate. But I would point out that for two places of decimals the methods Mr. Cammidge used are not accurate, and this might perhaps explain certain small differences which seemed to be unduly magnified. For instance, the ammonium sulphate method of precipitating total proteids would also give him uric acid mixed with them; and the magnesium sulphate method of precipitating globulin would not give him simply globulin, because magnesium sulphate produces a precipitate of inorganic substances in perfectly normal urine. So I think before we proceed to lay down any rules regarding this subject, it would be necessary that experiments should be performed with absolutely trustworthy tests. So far as they go, the numbers which Mr. Cammidge brought before us support entirely the view that, except in quite occasional cases, albumin comes through very much more readily than globulin.

I am afraid it is too late to try and attempt an answer to Dr. Weber's difficulties. The question that Dr. Weber raised, must, of course, be investigated, not by the simple tests which he described, but by collecting large quantities of the materials in question, and only then will it be possible to determine whether they are mucins. With regard to the passage of hæmoglobin, which was one of the points raised by Dr. Garrod, it shows, I think, what a very huge molecule the ordinary proteids

must have. Hæmoglobin is one of the proteids or proteid-like substances of which a determination has been made of the molecular weight. This is stated to be somewhere over 16,000, and, according to both clinical and experimental observations, it goes through the kidney cells with comparative ease. If the number just given is correct, we can realise what an enormous molecule it is which will not go through, but which is stopped by the kidney cells.

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19. *On the pathology of diabetic coma.*

By KARL GRUBE, M.D. (Neuenahr, Germany).

From the Research Laboratories of the Royal College of Physicians, London, and Royal College of Surgeons, England.

THE following paper contains the results of a series of experiments that have been performed with the object of obtaining some information on the causes that produce diabetic coma. This condition has a great practical importance, as not a few diabetics die in coma; it is not yet fully understood, nor have we any means of successfully treating it. We have quietly to stand by if one of our diabetic patients is seized with coma, as the treatment proposed for it has, at the best, only a temporary effect.

A great deal of work has been done during the last few years to clear away the mist that still surrounds the pathology of diabetic coma, and before relating the results of my experiments it may not be uninteresting to sketch in brief outlines the various theories that have been brought forward to explain its occurrence and its symptoms.

A great many diabetics die in coma. Although young diabetics suffering from the severe form of the disease supply a higher percentage, it must be admitted that coma, like the sword of Damocles, is hanging over every diabetic patient.

The first mention of coma as the fatal end of diabetes is to be found, I think, in a still instructive and valuable paper by *Marsh*.[1]

[1] 'Dublin Quarterly Review,' 1854, xvii, p. 1, "Observations on the Treatment of Diabetes Mellitus."

Diabetic coma generally sets in with a disturbance of digestion, consisting in failing appetite, vomiting, and diarrhœa. The patient rapidly loses strength; the urine generally contains, besides sugar, large quantities of acetone, diacetic acid, β-oxybutyric acid, and ammonia; there is usually albuminuria. The breath has the peculiar sweet smell due to acetone. When these symptoms have lasted for a day or two the patient becomes drowsy and gradually passes into coma. Sometimes a stage of great excitation precedes the drowsiness, the patient becomes restless, with flushed face and high and rapid pulse. After some hours coma sets in or, as I have sometimes observed, convulsions occur followed by coma.

The characteristic feature in many cases of diabetic coma is the peculiar respiration, first described by *Kussmaul*.[1] This peculiar respiration begins usually some time before the coma makes its appearance, and it is even sometimes the first sign that coma is impending. It is a form of dyspnœa consisting in very deep inspirations. The air is drawn in with great force; the thorax is expanded *ad maximum* with every inspiration and the entering air produces a peculiar sighing noise. The expirations are shorter. The frequency of the respirations may be increased or diminished. Towards the end the respiration becomes gradually more shallow and frequent. The patient dies at last from respiratory paralysis.

The tongue is dry and hard; the temperature of the body is lower than normal. The pulse and the action of the heart are, except in cases of great emaciation and weakness, strong and frequent. The reflexes remain unchanged to the last.

The foregoing description gives the symptoms which I have observed in nine cases of typical diabetic coma.

Various theories have been brought forward to explain this condition.

1. *Acetonæmia.—Petters*[2] and *Kaulich*[3] first discovered the presence of acetone in the urine and blood of comatose diabetics, and they regarded the coma as a poisoning by acetone. This view is still adhered to by some writers. I think it to be erroneous from the following reasons:—(*a*) diabetics may excrete

[1] 'Deutsches Archiv für klinische Medicin,' 1874, xiv.

[2] 'Prager Vierteljahrschrift,' 1857.

[3] Ibid., 1860.

large quantities of acetone for years without showing any sign of coma; (*b*) cases have been observed in which acetone disappeared from the urine as coma set in; the latter, therefore, does not depend on the presence of acetone; (*c*) experiments have shown that acetone has no poisonous effect, except in very large doses, and the symptoms it then produces are not those of coma.

2. *Uræmia.*—I can dismiss in a few words the theory which looks upon diabetic coma as a form of uræmic poisoning. Uræmic coma differs essentially from the typical diabetic coma. The former is always due to disease of the kidneys, while in the latter the condition of the kidneys is only of secondary importance. Of course, a patient suffering from diabetes may die from uræmia, but in that case he is also the subject of a severe form of renal disease, and to this the fatal end is due, not to diabetes.

3. *Acidosis*, or poisoning by acid formation.—*Stadelmann* was the first to explain[1] diabetic coma as the consequence of increased acidity of the blood and tissues. Previous to him *Hallervorden* had found that in severe cases of diabetes an excessive amount of ammonia was excreted, and he believes this increase to be due to an increased formation of acids, but it is the merit of *Stadelmann* to have first demonstrated that an abnormal acid was present. He believed it to be α-krotonic acid; we now know by the work of *Minkowski* and *Külz* that the acid formed is β-oxybutyric acid. This theory of *Stadelmann* seems to be supported by experiments of *Walther*,[2] who found that by giving hydrochloric and phosphoric acid to rabbits a condition somewhat similar to diabetic coma could be produced.

Besides β-oxybutyric acid various other acids, as diacetic, lactic, and fatty acids, are supposed to concur in the production of acidosis and diabetic coma.

This theory has been of practical value in so far as it has led to the treatment of this condition by large doses of bicarbonate of soda.

4. *Toxæmia.*—This theory assumes that in the last stages of

[1] 'Archiv f. experim. Pathol. und Pharm,' xvii, 443; and 'Deutsches Archiv f. klin. Med.,' xxxviii, 580.

[2] 'Arch. für experim. Pathol. und Pharm.,' vii, 148.

diabetes a poison of yet unknown nature is formed which produces coma, while the appearance of the various substances we have named is only symptomatic. This poison, which probably would be the product of abnormal proteid metabolism, would therefore be the common cause of the coma and of the substances which appear in this condition in the urine (*Klemperer*).

We have now to consider a paper which has been recently published by *W. Sternberg*.[1] The author in this paper describes experiments which he performed on animals with a substance that he believes to be the unknown toxin of *Klemperer* and others.

It has been shown by experiments that β-oxybutyric acid, diacetic acid, and acetone themselves are not poisonous, but their presence in the urine of comatose diabetics suggests that they may be the products of decomposition of another substance which itself is poisonous. Considering the symptoms of diabetic coma, *Sternberg* came to the conclusion that the substance in question ought to belong to the amido-bodies, and considering further that *Binz* and *Mayer* had succeeded in producing a condition similar to coma by injecting butyric acid, he further concluded that the looked-for substance might be amido-butyric acid, and assuming that β-oxybutyric acid was one of the products of decomposition of the hypothetical poison, the amido-butyric acid could only be the β-amido-butyric acid. *Sternberg* in this way arrived theoretically at the conclusion that β-amido-butyric acid must possess all the qualities necessary to produce diabetic coma. Having advanced so far, there remained only for him to prove by experiments that by giving this acid to animals a condition similar to diabetic coma could be produced, and it is sufficient to say that he succeeded in doing so to a certain extent.

The subject, as everybody will admit, is important enough to call for more experimental evidence, with a view of testing *Sternberg's* results and discovering if it is possible:

1. To produce coma.

2. To produce a respiration identical or similar to that appearing in diabetic coma.

3. To show the presence in the urine of those substances we

[1] 'Zeitschrift für klinische Medicin,' xxxviii, 65.

find in the urine of comatose diabetics, to wit, β-oxybutyric acid, diacetic acid, and acetone.

My experiments, with one exception, were performed on cats; they are twelve in number.

The cats were brought under a mixture of alcohol, chloroform, and ether; a cannula was fixed in the left jugular vein, while another in the right carotid was connected with a manometer to record the blood-pressure. A tambour was fixed over the abdomen to record the respiratory movements. While the animal was still under the anæsthetic the injection of β-amido-butyric acid into the jugular vein was begun.

The acid used was obtained from Dr. Schuchardt, in Görlitz; it contained about 90 per cent. of free acid. It was made slightly alkaline by adding a little ammonia. In each experiment the quantity of acid used was weighed, dissolved in distilled water, and injected slowly from a burette, care being taken only to inject small quantities of fluid at a time.

The effects on the animals were very striking and as follows:

1. Narcosis was soon obtained; it deepened as the injections increased in number, and was sometimes absolute. The reflexes remained normal.

2. Soon after the injection the pupils were dilated. This dilatation lasted a considerable time, and was then followed by contraction.

3. The respiration was much altered; soon after the injection had begun the respiratory movements became deeper and generally quicker. The inspiratory movements were chiefly affected; they became deeper and stronger, especially after some time, and when large quantities of acid had been injected. In some instances the respiration became slower; in one instance as slow as 18 in the minute, while the ordinary frequency in a cat is about 36. In those cases in which the animal was kept alive for several hours the respiration towards the end became more shallow. The type of the respiration was also altered; the expansion of the chest was much more forcible than is normal in the cat.

4. Soon after the injection the heart beat more quickly and strongly and the blood-pressure was considerably increased; this high blood-pressure remained pretty constant through the whole experiment.

5. Urine was obtained in nine cases; it was tested for sugar eight times, for diacetic acid nine times, and for acetone five times.

(*a*) Sugar was found seven times, sometimes in considerable quantity. In the one experiment in which it was not found the cat had been starved for four days previously to the experiment. This was done to produce the condition of "subnutrition," in which all diabetics are, in their last stage, and to see whether the influence of the acid was more marked. This it was not, and the starvation was therefore not repeated. The presence of the sugar was probably due to the operation.

(*b*) Diacetic acid (tested for by Gerhardt's reaction) was present in eight cases. In the one instance in which it was not found the experiment had lasted only a very short time. The amount of diacetic acid increased with the duration of the experiment.

(*c*) Acetone was present four times, and only in those experiments which lasted a considerable time. In one case the urine was tested in the beginning of the experiment after the first injection, when it was found to be free from acetone and diacetic acid, while that taken from the bladder after the experiment had terminated contained both.

From these experiments it will be seen that it was possible to produce by the injection of β-amido-butyric acid:

1. Coma.

2. An alteration of the respiration similar to that occurring in diabetic coma.

3. To show the presence in the urine of diacetic acid and acetone.

I think it, therefore, quite safe to say that β-amido-butyric acid may be the substance or one of the substances which produce diabetic coma. Further investigations will, I hope, furnish more information on this point. *March 6th*, 1900.

20. *A preliminary note on the indol-like reaction given by cultures of the diphtheria and of the pseudo-diphtheria bacillus.*

By RICHARD T. HEWLETT.

(From the Jenner Institute of Preventive Medicine.)

CONTRADICTORY statements have been made with regard to the presence of indol in, or of an indol reaction obtained with, cultures of the diphtheria bacillus. The distinction is a necessary one, for it is not sufficient to obtain the indol-red reaction with a nitrite and acid to prove the presence of indol; substances other than indol give the indol-red reaction.

Petri,(1) Kitasato,(2) and Theobald Smith,(3) employing twenty-four to forty-eight hours' bouillon cultures of the diphtheria bacillus, did not obtain any indol-red reaction; and Lewandowski,(4) by distilling eight to ten days old cultures and testing the distillate, was unable to detect any indol.

On the other hand, Palmirski and Orlowski(5) state that an indol reaction can be obtained with diphtheria cultures feebly after a few days, markedly after two or three weeks. In Flugge's text-book ('Die Microorganismen,' 3te Auflage, p. 462) it is stated that Peters has confirmed the observations of these observers, but I have been unable to refer to the original paper. Miss Knight and myself (6) likewise obtained distinct indol reactions with cultures both of the diphtheria and of the pseudo-diphtheria (Hoffmann) bacillus after two to three weeks' growth.

In view of these conflicting results I have recently examined a number of cultures from several strains, both of the diphtheria and of the pseudo-diphtheria bacillus.

I find that the cultures always give the indol-red reaction with a nitrite and hydrochloric acid. The reaction is not obtained under about four days' growth, but becomes well marked in cultures two to three weeks old, cultures of the diphtheria bacillus giving a better reaction than those of the pseudo-diphtheria bacillus. Cultures of both organisms giving good indol-red reactions were next distilled to ascertain whether indol was present; the distillates, carefully tested, and in some cases re-distilled before testing, never gave a trace of an indol reaction,

and therefore the substance giving the reaction is not indol. I am now attempting to isolate this substance, which is possibly skatol-carbonic acid, for it is non-volatile, and it gives the red reaction with perchloride of iron and hydrochloric acid. It is, however, but slightly soluble in ether, more soluble in alcohol; and so far I have not obtained the purple reaction with chloride of lime and hydrochloric acid said to be given by skatol-carbonic acid,(7) so that not improbably it is some other compound.

The substance appears to be formed under much the same conditions as indol is by other bacteria; for example, it is more abundant in media rich in proteids, while glucose and glycerine inhibit its formation.

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May 1st, 1900.

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21. *A new quantitative method for serum diagnosis.*

By RICHARD T. HEWLETT and SYDNEY ROWLAND.

(From the Jenner Institute of Preventive Medicine.)

FOR the successful application of the agglutination test (Widal method) in the diagnosis of disease, or for the recognition of bacteria and the testing of experimental sera, some dilution of the blood is desirable or necessary—a dilution which should be approximately known for clinical purposes, and which it should be possible to estimate with accuracy in all experimental work. Of the various methods employed for diluting the following may be mentioned.

1. *Dilution by means of a platinum loop* (McWheeny, Delé-

pine, and others).—This at the best can be but approximate, as not only is it practically impossible to maintain uniformity in the construction of loops, but, in addition, the amount of fluid taken up by a loop varies according to many factors, such as viscosity, cleanliness of the loop, etc.

2. *Dilution by means of a capillary pipette* (Wright).—This method has some disadvantages. It is very difficult to maintain a capillary pipette in a uniform condition of cleanliness; and in dealing with coagulable fluids, unless the greatest care be taken, minute coagula are liable to remain in the lumen of the pipette and seriously impair its accuracy,—and in those cases where the examination of the whole blood must be made some time after its collection, the use of any method of direct volumetric estimation is prohibited.

3. *The dry blood method* (Johnson).—In this method the blood is spotted on to aluminium foil, and when dry a milligramme is weighed out and diluted. It is assumed that the blood loses 75 per cent. of its weight on drying. Obviously this method is subject to many inaccuracies, *e. g.* variability in the amount of solids in the blood and in the dryness of the film, whilst the weighing out of so small a quantity as one milligramme is both tedious and inaccurate.

4. *The hæmoglobinometric method* (the blood being dilute to a given standard of colour).—This method is not accurate considering the great variations that take place in the hæmoglobin of blood in health and disease.

5. *The capillary tube method* (McFarland).—McFarland makes use of capillary tubes of a standard size, which are calibrated by comparing the heights to which a given solution is raised in their lumen by capillary action.

This method labours under the disadvantage that it is impossible to obtain capillary tubes of even approximately the same internal diameter, as can easily be demonstrated by directly measuring the diameter of tubes which the above method has indicated to be of the same bore. This discrepancy is accounted for by the large number of disturbing factors influencing the capillary rise of liquids in tubes of small diameter. This is illustrated in the following example. Out of eight tubes shown to be of equal diameter by the above capillary method, no two had the same diameter. The actual measurements varied from

1·050 mm. to 1·140 mm. In two tubes of unit length this difference in diameter would give an error of nearly 15 per cent. in the volume of the contained blood.

We do not mean to imply that the above methods are entirely useless, for all of them give more or less satisfactory results for rapid clinical diagnosis, or in those cases where an approximation suffices, but we believe that the capillary pipette method (No. 2 above) is the only one which has any claims to accuracy. We have therefore devised the following quantitative method, which is suitable not only for serum, but also for the whole blood, and is capable of the greatest accuracy. Ordinary vaccine tubes are taken, the large, the very small, and any irregular ones being discarded. We prefer those varying in diameter from about 0·9 mm. to 1·2 mm. They are thoroughly cleaned by boiling in strong nitric acid, rinsing in tap and then in distilled water, and are then dried and sterilised. A large number can thus be treated at one operation. If great accuracy is desired the tubes should be examined microscopically at a low power to ascertain whether they are regular in section, and, for the most delicate estimations, can be calibrated by partially filling with distilled water, weighing, and so ascertaining the volume, and in this way checking the volume to be deduced from the measurements to be described hereafter.

The selected tubes are charged with the blood to be examined, being preferably half to two thirds filled, and are carefully sealed by melting the ends in the flame in the ordinary way. In order to ascertain the volume of the blood, the length of the column of blood is first measured by means of a scale graduated to half-millimetres, assisted by a lens mounted to avoid parallax. In practice it is sufficiently accurate to measure between the convexities of the menisci. The sealed ends of the tube are then cut off by means of a fine file or cutting diamond as near the column of blood as practicable, and the internal diameter measured. This is carried out in the following manner. The tube is supported in the axis of the microscope by means of two inch diaphragms, carried respectively by the stage and the substage. These close concentrically and support the tube, at the same time cutting off all light reflected from the mirror except that which can pass up the solid walls of the tube, the lumen of the tube being obstructed by the blood. In the field of the micro-

scope the lumen of the tube now appears as a black circle surrounded by a brilliantly illuminated ring. Owing to the extreme sharpness of the image, the measurement of the diameter of the tube can be carried out with great accuracy by means of an eyepiece micrometer arranged to give readings to the one thousandth of a millimetre. From the formula—

$$V. = D.^2 \times L. \times 0{\cdot}7854,$$

where V. = volume of cylinder of blood, D. = diameter of the cylinder of blood, L. = length of cylinder of blood, the volume of the blood is calculated. As it is of the utmost importance that the diameter of the tube be accurately measured, the adjustment of the eyepiece micrometer must be carried out with great care, and the scale by which it is set should be one the accuracy of which is undoubted; for from the formula ($V. = D.^2 \times L. \times 0{\cdot}7854$) it will be seen that any error in the measurement of D. will be increased in a geometrical ratio in the final result, hence the comparative inefficiency of a capillary tube method in which D. is measured indirectly with less accuracy.

The accuracy of this method of estimating the volume has been controlled as follows: Selected tubes were weighed, then partially filled with distilled water and sealed. By again weighing and subtracting the weight of the empty tube the weight of the water in the tube was ascertained (and so the volume). The volume of the distilled water was then estimated directly by measuring the length of the column of water and the diameter of the tube. The following are some of the results obtained:

Tube.	Vol. of Aq. by weight.	Vol. of Aq. by measmt.	Percentage of error.
1	0·0290	0·0294	1·38 +
2	0·0310	0·0311	·3 +
3	0·0328	0·0331	·91 +
4	0·0314	0·0311	·64 −
5	0·0246	0·0247	·4 +
6	0·0676	0·0681	·77 +

It is desirable, when possible, that the column of blood should be unbroken, for although the method can still be carried out, the measurement of each separate portion of the column is liable

to introduce error. With regard to the length of the column of blood, this remains practically unaltered in a sealed tube for days or even weeks.

Having ascertained the volume of blood, it remains to carry out the dilutions; this is accomplished as follows:

The capillary tube is placed in a vertical thick-walled glass tube of slightly larger bore, the lower end of which is submerged in the required amount of the diluting medium (measured out by a graduated pipette) contained in a hollowed block of glass, such as is used in histological and microscopical work. The capillary tube with its contained blood is then crushed *en masse* by means of a soft iron plunger, and the interior of the containing tube is washed out several times by drawing up the diluting medium into its lumen, either with the mouth or by means of an india-rubber teat. The powdered glass quickly falls to the bottom, and the mixture may be employed for conducting the serum reaction either by the microscopic or the macroscopic method. *May 1st*, 1900.

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22. *On a hæmolysin in cultures of* Bacterium pyocyaneum, *and an antihæmolytic body in the serum of immunised animals.*

By William Bulloch and William Hunter.

The recent work of Bordet, Ehrlich, and Morgenroth and others on the hæmolytic properties acquired by the blood-serum of animals treated by the subcutaneous injection of the red blood-corpuscles of other animals has thrown much light upon the important question of bacteriolysis. It is also well known that certain poisons, both animal and vegetable, produce a solution of the red blood-corpuscles and the passage of the hæmoglobin into the fluid. We need only refer to the serum of the eel, cobra-venom, and certain vegetable poisons, especially phallin, ricin, and crotin. Among the bacteriogenetic poisons, hæmolytic bodies have been discovered by Ehrlich and Madsen in the case of *Bacillus tetani*. As shown by Madsen, there exists in tetanus antitoxin a body

which neutralises *in vitro* the hæmolytic properties of the tetanolysin, the anti-tetanolysin being distinct from the anti-tetanospasmin. Our experiments have dealt with cultures and filtrates of *Bacterium pyocyaneum*. The organism used by us in these experiments had a virulence such that ·1 c.c. of a bouillon culture killed a guinea-pig of 500 grammes weight in less than twelve hours.

In three filtered cultures of this organism we have found a poison which dissolves the red corpuscles of the ox, sheep, rabbit, monkey, cat, dog, and rat. The hæmolytic effect takes place the more quickly the higher the concentration of the toxine, but in any case there appears to be a latent period at the commencement during which there is no hæmolysis. In the serum of a goat actively immunised by Dr. Dean with the filtrates of *Bacterium pyocyaneum* we have also found an antihæmolytic body which neutralises *in vitro* the effects of the *pyocyaneus* hæmolysin and prevents the solution of the red corpuscles. The following remarkable result has, however, been repeatedly observed. With small doses of the immune serum hæmolysis occurs; with medium doses no hæmolysis (*i. e.* the effects of the hæmolysin are neutralised); whereas with large doses of serum hæmolysis again is encountered, these results being to a certain extent analogous to the results of animal experiments obtained by Wassermann.

The technical procedure used in carrying out the experiments was as follows:—Perfectly fresh defibrinated ox blood was made into a 5 per cent. suspension with isotonic salt solution. By means of graduated standard pipettes varying quantities of *pyocyaneus* toxine were put into test-tubes, and to each test-tube were added two cubic centimetres of the 5 per cent. suspension of corpuscles; the tubes were then incubated overnight and the result estimated in from eighteen to twenty hours. In the case of the serum experiments the toxine and serum in carefully measured quantities were mixed, and to the mixture the red corpuscles were then added. In eight different filtrates examined in this way we have demonstrated the existence of the hæmolysin in three. *May 1st*, 1900.

23. *On the interaction of toxine and antitoxine; illustrated by the reaction between cobralysin and its antitoxine.*

By WALTER MYERS.

From the Pathological Laboratory, Cambridge.

IN the venom of the *Cobra capella* there are present at least two poisonous substances. One of these is hæmolytic, the other causes death, probably by its action on the respiratory centre in the medulla oblongata. For the sake of convenience we may call these poisons *cobralysin* and *cobranervin* respectively. We have the following reasons for considering these two poisons to be distinct one from the other:

1. Their different behaviour towards heat.—Weir Mitchell and Reichert showed some years ago that the hæmolytic poison is precipitated and destroyed by heat before the nerve poison is affected.[1]

2. The behaviour of cobra venom with antivenomous serum. —It may happen that the cobralysin is neutralised by the antitoxine, whereas the cobranervin remains free. It is only for the minimal lethal dose, or a little over (using guinea-pigs as test animals), that the neutralisation of the two effects runs hand in hand.[2] With multiples of the minimal lethal dose a non-hæmolytic mixture of venom and antivenom may kill a guinea-pig fairly rapidly. These facts are evidence that the two poisons are distinct, and that a serum may possess an antilysin, which, considered in relation to a particular venom, is in excess of the antinervin.

3. The susceptibility, *in vitro*, of the red corpuscles of various animals bears no relation to the susceptibility of those animals to subcutaneous inoculation of the venom. In the lethal properties of the venom the cobralysin plays an insignificant part.

By the study of the neutralisation of diphtheria toxine by its

[1] Weir Mitchell and Reichert, 'Smithson. Contrib. Knowl.,' Washington, 1886.

[2] Stephens and Myers, 'Journ. Path. and Bacteriol.,' Edinburgh and London, 1898, vol. v, p. 279.

antitoxine[1] Ehrlich has shown that this is a very complicated process, and that we may explain it by the assumption of various bodies in the toxine. These results have been confirmed by Madsen,[2] and in this country by Cobbett[3] and by Bulloch.[4] Madsen[5] has found similar phenomena in the neutralisation of tetanolysin by its antitoxine.

In this country the analyses of toxines have been performed by Ehrlich's old method of calculation from L_o and L+. In this way, however, important facts concerning the toxine are not brought to light, and his new method may here be shortly described.

It consists in a partial neutralisation of the L_o dose, and a determination of the number of lethal doses which are thus left free. The L_o dose is that quantity of toxine which is completely neutralised by one unit of antitoxine. By partially neutralising the poison some toxine and toxoids are left free, and by this means we are able to determine the relative and absolute quantities of these substances which remain uncombined with the antitoxine. As the only toxines so far investigated are diphtheria and tetanolysin, the behaviour of cobralysin with its antitoxine was studied with this in view.

Measurement of the Cobralysin.

The first step in the investigation was to find a reliable method for the measurement of the amount of cobralysin present in a given quantity of fluid. This is done by estimating its action on the red corpuscles of a certain blood, under fixed conditions of concentration, temperature, and time. With cobralysin, however, certain difficulties arise. In the first place, only small quantities of the poison can be used, as the venom is difficult to obtain, and as the neutralising power of the antivenomous serum at present on the market is by no means great. To abolish the hæmolytic action of 1 mgrm. of the venom I worked with, for

[1] Ehrlich, "Die Werthbemessung des Diphtherieheilserums," 'Klin. Jahrb.,' Berlin, 1897, Bd. vii, S. 299; "Ueber die Constitution des Diphtherie Giftes," 'Deutsche med. Wochenschr.,' Leipzig, 1898.

[2] "La Constitution du poison diphthérique," 'Ann. de l'Inst. Pasteur,' Paris, 1899, tome xiii, p. 568.

[3] "The Origin of Antitoxine," 'Lancet,' London, 1899, vol. ii, p. 332.

[4] 'Trans Jenner Inst.,' London, 1899.

[5] 'Zeitschr. f. Hyg.,' Leipzig, 1899, Bd. xxxii, S. 214.

example, it was necessary to employ 1 to 2 c.c. of undiluted serum. Hence one cannot use quantities of venom greater than 1 mgrm., for the amount of antitoxic serum which must be used for neutralisation would become inconveniently large. Most serious, however, is the second difficulty. Most horse sera hæmolyse guinea-pig's red corpuscles. Now the most susceptible corpuscles amongst the common laboratory animals are those of the guinea-pig and the dog; hence one of the animals most suitable as an indicator for the cobralysin was put out of court. The rabbit's corpuscles are less susceptible to the cobralysin than those of the guinea-pig; and a few preliminary trials showed that far too much poison would be necessary were this blood used, though in other respects it is well suited for the purpose.

In measuring the action of a hæmolytic poison, it must be borne in mind that the red blood-corpuscles are by no means uniform. They show, as might be expected from their different ages, varying degrees of susceptibility. This varying susceptibility has been noted by several observers.

These variations are well shown by the following experiment. Defibrinated rabbit's blood was centrifugalised, and the serum removed from the corpuscles. They were washed with 0·8 per cent. salt solution, and then suspended in salt solution of this strength. The action of the poison was tested on suspensions, made up to the strengths of one part of original blood in five of salt solution, one in ten, and one in twenty respectively. The tubes were left at the laboratory temperature for eighteen hours. The following table shows the results obtained:

TABLE I.

	1 c.c. blood.		
Mgrms. venom in 1 c.c.	$\frac{1}{20}$.	$\frac{1}{10}$.	$\frac{1}{1}$.
1	$\frac{1}{200}$	$\frac{1}{100}$	...
0·5	H.	...	$\frac{1}{50}$
0·25	„	$\frac{1}{200}$	$\frac{1}{100}$
0·1	„	H.	...
0·05	„	„	$\frac{1}{200}$
0·025	„	„	H.
0·01	Trace H.	„	„
0·005	„	„	„
0·0025	„	? H.	? H.

From this table we see that with a suspension of blood of $\frac{1}{20}$ the amount of poison necessary for destruction of the corpuscles, to the extent equivalent to the solution of 1 part of blood in 200 of water, was 1 mgrm. With $\frac{1}{10}$ blood the amount was 0·25 mgrm., with $\frac{1}{20}$ blood, 0·05 mgrm. In other words, with the same concentration of cobralysin, the more blood there is present the greater is the hæmolysis. The amount of hæmolysis, however, is not proportional to the strength of the blood suspension, but is much greater. This seemingly paradoxical result is obviously caused by the presence of the more susceptible corpuscles. In the more concentrated suspensions of blood more of these corpuscles are present; hence the hæmolysis is greater.

This experiment further shows the necessity of using the same amounts of blood in measuring the action of the cobralysin, and, as the result of several trials, the following method was adopted:—The poison was weighed out freshly for each experiment from the stock tube of dry venom. It was dissolved in 0·8 per cent. salt solution, and carefully protected from the light and from evaporation. Small test-tubes were used, and in each 1 c.c. of poison, containing varying amounts of the dry venom, was placed. A standard platinum loop was used for all the experiments, and one loopful of human blood, taken as it came from a finger prick, was suspended in the fluid. The tubes were left at laboratory temperature, and the result was noted at the end of eighteen hours. The point used for measurement was the last tube which showed any hæmolysis; and repeated experiments showed that by this method an accurate way of measuring the action of the cobralysin had been obtained.

The Neutralisation of the Cobralysin by Calmette's Antivenomous Serum.

As has already been mentioned, Ehrlich's method of examining the neutralisation of a toxine consists in neutralising a high multiple of the minimal lethal dose, and in determining the number of lethal doses which are left free when a less amount of antitoxine is used than that required for complete neutralisation. In the case of the cobralysin, the minimal hæmolysing quantity for human blood was found to be 0·0003 to 0·0005 mgrm. A perfectly arbitrary amount, namely, 1 mgrm., was chosen for

neutralisation, and the amount of antitoxine required to neutralise this amount was determined. It was necessary for this purpose to use undiluted antivenomous serum. Several bottles of serum were mixed together, and the stock bottle kept in a cool dark cellar. The serum was assumed to remain constant in antitoxic power for three days, during which time the examination of a poison could be performed.

Fraser in 1896,[1] and Martin and Cherry[2] later, have shown that the reaction between cobranervin and its antitoxine takes a considerable time. The following experiment shows that the union of cobralysin and its antitoxine also takes a measurable time:

To 0·5 c.c. of a solution of dry venom, containing 1 mgrm., 0·2 c.c. of antitoxine was added. Several mixtures of this kind were made and examined for their hæmolytic powers immediately, a quarter of an hour, one hour, and two hours after

TABLE II.

Mgrms. of poison in 1 c.c.	Control 1.	1 mgrm. venom + 0·2 c.c. A. V. Serum, mixed and examined.				Control 2, after 2 hours.
		At once.	After 15 minutes.	After 1 hour.	After 2 hours.	
0·01	...	...	...	H.	H.	...
0·008	...	...	...	„	„	...
0·006	...	...	...	„	„	...
0·005	...	H.	H.	„	„	...
0·004	...	„	„	No H.	No H.	...
0·003	...	„	„	„	„	...
0·0025	...	„	„	„	„	...
0·002	...	„	„	„	„	...
0·0017	...	„	No H.	„	„	...
0·0013	...	„	„	„	„	...
0·001	H.	No H.	„	...	...	H.
0·0008	„	„	„	...	...	„
0·0006	„	„	...	...	...	„
0·0005	„	...	...	...	...	„
0·0004	„	...	...	...	...	No. H.
0·0003	No H.	...	...	...	...	„
0·00025	„	...	...	...	...	„
0·0002	„	...	...	...	...	„
0·00017	„	...	...	...	...	„
0·00013	„	...	...	...	...	„
Control saline	„	...	...	...	...	„

[1] 'Nature,' London, 1896, vol. liii.

[2] 'Proc. Roy. Soc. Lond.,' 1898, vol. lx, p. 88.

mixing. A control with poison alone was made at the beginning and at the end of the experiment, the poison being allowed to remain, like the other mixtures, at room temperature (15° C.), carefully protected from light and from evaporation. The control poison, which stood at room temperature, was of the strength 1 c.c. = 2 mgrms. As will be seen from the preceding table, the control had not undergone any weakening of importance during this time. The interaction of the toxine and antitoxine, however, was markedly incomplete immediately after mixing, and even after fifteen minutes. No difference could be observed between the completeness of the reaction after one hour and two hours.

TABLE III.

Mgrms of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.				
		0·1 c.c.	0·2 c.c.	0·4 c.c.	0·6 c.c.	0·8 c.c.
0·15	...	...	...	...	...	H.
0·13	...	...	...	...	...	„
0·1	...	...	...	...	...	„
0·08	...	...	...	...	...	„
0·06	...	...	...	...	H.	„
0·05	...	...	...	H.	„	„
0·04	...	...	...	„	„	No H.
0·03	...	...	...	„	„	„
0·025	...	...	H.	„	„	„
0·02	...	...	„	„	„	„
0·017	...	...	„	„	No H.	...
0·013	...	H.	„	„	„	...
0·01	...	„	„	„	„	...
0·08	...	„	„	No H.	...	...
0·06	..	„	„	„	...	...
0·005	...	„	„	„	...	...
0·004	.	„	No H.	...	...	...
0·003	...	„	„	...	...	...
0·0025	...	„	„	...	...	...
0·002	...	No H.	...	...	...	...
0·0017	...	„	...	...	...	...
0·0010	H.	„	...	...	..	...
0·0008	„	„	...	...	...	...
0·0006	„	„	...	...	...	...
0·0005	„	...	...	...		...
0·0004	No H.	...	...	...	...	...
0·0003	„	...	...	...	...	...
0·00025	„	...	...	...	...	...
0·0002	„	...	...	...	...	...
Control saline	„	...	..	...	...	...

In this table H. signifies hæmolysis, No H. the absence of hæmolysis.

In the experiments in this paper, the mixtures of venom and antitoxine were allowed to stand at laboratory temperature for two hours before testing their action on blood. The control tubes also remained for the same time under similar conditions.

In order to neutralise 1 mgrm. of this venom for hæmolysis, 1·3 c.c. of antivenomous serum was required. In order to investigate the neutralisation of the poison, less than this quantity was added, and the amount of free cobralysin estimated by determining the minimal hæmolysing dose of these mixtures. Table III shows the results thus obtained.

We may sum up the results in the following:

TABLE IV.

	Minimal hæmolysing dose in mgrms. of dry venom.
Venom alone	0·0005 mgrm.
1 mgrm. venom + 0·1 c.c. serum	0·0025 „
1 „ „ + 0·2 „ „	0·005 „
1 „ „ + 0·4 „ „	0·008 „
1 „ „ + 0·6 „ „	0·017 „
1 „ „ + 0·8 „ „	0·05 „

As has already been mentioned, 1·3 c.c. of the serum employed was necessary to neutralise the cobralysin contained in 1 mgrm. of dry venom.

We see, then, that when we add one-thirteenth of the serum necessary to neutralise the cobralysin, the minimal hæmolysing dose rises from 0·0005 mgrm. to 0·0025 mgrm., a quantity five times as great. The venom, in other words, has lost four fifths of its toxic action. On adding 0·2 c.c. of serum, or about one sixth of the serum necessary for complete neutralisation, we have raised the minimal hæmolysing dose to 0·005 mgrm.; or, in other words, we have taken away nine tenths of its hæmolytic power.

We see at once from these results that the interaction of the cobralysin and its antitoxine is very different from that of a simple neutralisation say of an acid by a base. For in this case, as is shown by every simple titration, the amount of acid which disappears is roughly proportional to the amount of base which is added.

We may summarise the above results in another way. One

mgrm. of poison contains $\frac{10,000}{5}$ or 2000 minimal hæmolysing doses. When 0·1 c.c. of antivenomous serum has been added, it now contains $\frac{10,000}{25}$ or 400. Now we will arbitrarily call the number of combining equivalents in 1 mgrm. of the poison 130. Hence, whilst removing ten equivalents from the poison we have removed 1600 hæmolysing doses. On the theory of simple neutralisation we should have removed $\frac{2000}{13} = 153$ hæmolysing doses.

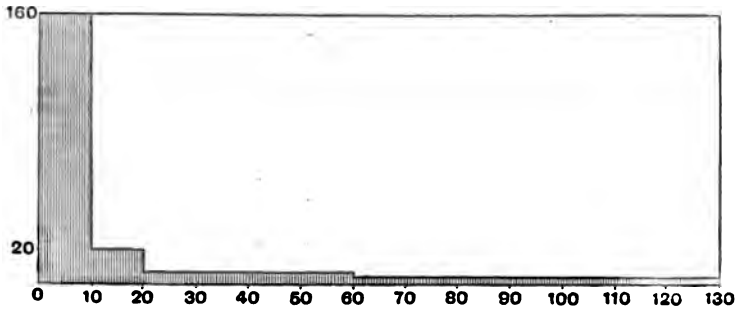
We may sum this up in the following table:

TABLE V.

Hæmolysing doses in 1 mgrm. of venom.		Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone . . .	2000			
„ + 0·1 c.c. A.V.S.	400	1600	10	160
„ + 0·2 „ „	200	200	10	20
„ + 0·4 „ „	125	75	20	3·75
„ + 0·6 „ „	58·8	66·2	20	3·3
„ + 0·8 „ „	20	38·8	20	1·9

We may most easily obtain a survey of this neutralisation process by putting these results in the form of a curve, as Ehrlich has done for diphtheria and Madsen for tetanolysin. From left to right we lay off the combining equivalents of the lysin, and in such a way that those furthest from the left are those which are last left free on incomplete neutralisation. We lay off 130 divisions on the horizontal line. When, for instance, 0·4 of the serum has been added, the toxine from 0–40 has been neutralised, that from 40–130 is left free. Now, from below upwards, we indicate the hæmolytic action, which in this case we divide into 160 parts. We are now able to represent the varying hæmolytic power of the poison as it is set free.

From 0–10 combining equivalents, each equivalent contains 160 hæmolysing doses. We then shade in the whole height of the chart in this place. From 10–20 we have only one-eighth to shade, since each equivalent corresponds to twenty hæmolysing doses. By this means we are able to see how much toxine is free with every degree of partial neutralisation of the venom.



Neutralisation chart (1). Venom A.

The examination of a second venom (B) yielded similar results. The facts are stated in the following tables:

TABLE VI.

Mgrms. of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.			
		0·05 c.c.	0·1 c.c.	0·2 c.c.	0·4 c.c.
0·1	...	...	...	...	H.
0·08	...	...	...	...	,,
0·07	...	...	...	...	,,
0·06	...	...	...	...	,,
0·05	...	...	...	...	,,
0·04	...	...	...	...	,,
0·03	...	...	...	...	,,
0·025	...	...	...	...	,,
0·02	...	...	...	H.	No H.
0·017	...	...	...	,,	,,
0·013	...	...	H.	,,	,,
0·01	...	...	,,	,,	,,
0·008	...	...	,,	,,	...
0·007	...	...	,,	,,	...
0·006	...	H.	,,	,,	...
0·005	...	,,	,,	No H.	...
0·004	...	,,	,,	,,	...
0·003	...	,,	,,	,,	...
0·0025	...	,,	No H.	,,	...
0·002	H.	,,	,,	,,	...
0·0017	,,	,,	,,	,,	...
0·0013	,,	,,	,,	,,	...
0·001	,,	,,	,,	...	...
0·0008	,,	No H.	...	...	...
0·0007	,,	,,	...	...	...
0·0006	No H.	...	...	...	...
0·0005	,,	...	...	...	...
0·0004	,,	...	...	...	...
0·0003	,,	...	...	...	...

TABLE VII.

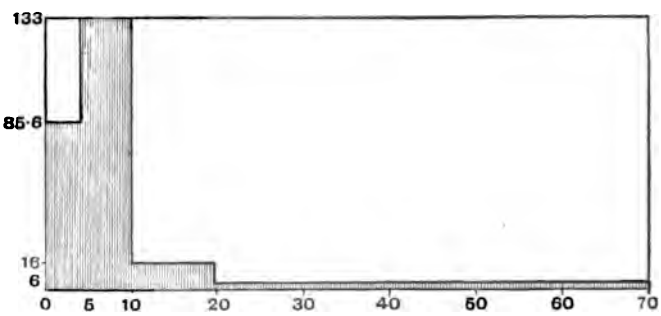
	Minimal hæmolysing dose in mgrms. of dry venom.
Venom alone	0·0007 mgrm.
1 mgrm. venom + 0·05 c.c. A.V.S. . . .	0·001 „
„ „ + 0·1 „ „ . . .	0·003 „
„ „ + 0·2 „ „ . . .	0·006 „
„ „ + 0·4 „ „ . . .	0·025 „

Now, 0·7 c.c. of antivenomous serum was required to neutralise 1 mgrm. of this poison. Arbitrarily, again, taking this to contain 140 equivalents, the following summary indicates the relation of hæmolytic to combining capacity in different stages of neutralisation:

TABLE VIII.

Hæmolysing doses in 1 mgrm. of venom.	Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone . . . 1428			
„ + 0·05 c.c. A.V.S. 1000	428	10	85·6
„ + 0·1 „ „ 333·3	666	10	133
„ + 0·2 „ „ 166·6	166	20	16
„ + 0·4 „ „ 40	126	40	6

The accompanying chart shows the relationships graphically:



Neutralisation chart (2). Venom B.

Comparison with the chart of neutralisation of Venom A shows that there is a striking similarity between the two. On the right

we have in each case poison which consists mainly of toxoid; towards the left, however, we have poison with a greater proportion of toxine; and still more to the left, toxine unaccompanied by toxoid. In this connection it may be noticed that Venom B in the portion which is last neutralised by the antitoxine contains some toxoid, whilst A does not contain any in this situation.

The charts have been drawn accurately to the tables from which they are made up. The poison seems from them to be made up of various parts of different toxicity. Thus, in the Chart of Venom A there seem to be four such parts. This appearance is merely due to the method employed. Were the measurements more numerous the chart would take the form of a curve sinking from left to right, and nearly parabolic in the case of A. In the case of B this curve would have a depression on its extreme left.

In these two poisons it will be noticed that different numbers have been taken for the numbers of combining equivalents in 1 mgrm. of dry venom. Now, though any one sample of dry venom remains constant for a very long time in hæmolysing power, 1 mgrm. of two different stocks contains varying numbers of hæmolysing doses. The two charts have been made on nearly the same scale for the purposes of comparison, but the figures given are not absolute but quite arbitrary. To obtain figures such as Ehrlich has given for diphtheria toxine, it would be necessary to examine a large number of venoms, and from the figures obtained to work out the absolute numbers. To do this we should naturally require a *standard serum*, and, it may be mentioned, an antitoxine of higher value than that of the antivenomous serum now issued from the Pasteur Institute at Lille.

The Formation of Toxoids.

Though fairly stable in concentrated solutions, in dilute solutions the weakening of the cobralysin takes place rapidly. A solution, for example, of dry venom, 1 c.c., containing 2 mgrms. in 0·8 per cent. salt solution, was kept in a cool cellar carefully protected from light and evaporation. After one week it was examined, with the results that are shown in Table IX. It should here be mentioned that in all these experiments, when not otherwise stated, Venom A was used, and that the serum was

TABLE IX.

Mgrms. of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.	
		0·1 c.c.	0·2 c.c.
0·02	...	...	H.
0·015	...	...	„
0·01	...	H.	„
0·008	...	„	„
0·006	...	„	No H.
0·005	...	„	„
0·004	...	„	„
0·003	H.	„	„
0·002	„	No H.	„
0·0015	„	„	...
0·0013	„	„	...
0·001	„	„	...
0·0008	No H.	...	...
0·0006	„	...	...
0·0005	„	...	...
0·0003	„	...	...
0·0002	„	...	...
0·0001	„	...	...
Control saline	„	...	...

the same as that employed in the experiments recorded in Table III; and further, that it was tested against 1 mgrm. of fresh venom, and found not to have altered in strength.

It is seen from Table IX that the minimal hæmolysing dose had doubled, and was 0·001 mgrm., whilst in the fresh poison it was 0·0005. With 1 c.c. of serum the minimal hæmolysing quantity is 0·003, and with fresh venom the corresponding quantity was 0·0025. The poison had not then undergone any change in its power of combining with antitoxine, as far as the equivalents saturated by 0·1 c.c. of it were concerned. Summarising these results as before, we get—

TABLE X.

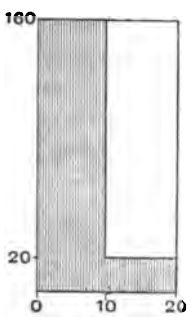
	Minimal Hæmolysing dose.
Venom alone	0·001 mgrm.
1 mgrm. venom + 0·1 c.c. A.V.S. . . .	0·003 „
„ „ + 0·2 „ „ . . .	0·008 „

Expressing the relationship between toxic action and combining power, we get—

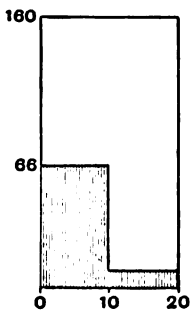
TABLE XI.

Hæmolysing doses in 1 mgrm. of venom.	Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone . . 1000			
„ +0·1 c.c. A.V.S. 333	666	10	66·6
„ +0·2 „ „ 125	108	10	10·8

Graphically expressed, we get the following figures:—On the left is a magnification of the first twenty combining units of Venom A. This is enlarged from Fig. 1, and represents values repeatedly obtained for this poison. On the right is the chart (Fig. 4) representing the results of table drawn to a similar scale:



Neutralisation of fresh venom.
Chart 3.



Neutralisation of venom after one week in cellar.
Chart 4.

It is evident that in the first ten equivalents we have a conversion of over one half of the toxine into toxoid, whilst in the combining equivalents, 10—20, we have a conversion of almost exactly half the toxine into toxoid.

Similarly, changes occurred when the venom was kept in the incubator at 35° C. for varying periods, as is shown in Tables XII to XX.

TABLE XII.—*One hour at* 35° C.

Mgrms. of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.		
		0·1 c.c.	0·2 c.c.	0·4 c.c.
0·025	...	...	...	H.
0·02	...	...	...	„
0·017	...	...	...	„
0·013	...	...	...	No H.
0·01	...	...	H.	„
0·008	...	...	„	„
0·006	...	...	„	„
0·005	...	...	No H.	„
0·004	...	H.	„	„
0·003	...	„	„	„
0·0025	H.	„	„	„
0·002	„	No H.	„	...
0·0017	„	„	„	...
0·0013	„	„	„	...
0·001	„	„	„	...
0·0008	„	„	„	...
0·0006	„	„	...	...
0·0005	No H.	„	...	...
0·0004	„	„	...	...
0·0003	„	...	...	...
0·00025	„	...	...	...
Control saline	„	...	...	...

TABLE XIII.

	Minimal Hæmolysing dose.
Venom alone	0·0006 mgrm.
1 mgrm. venom + 0·1 c.c. A.V.S. . . .	0·0025 „
1 „ „ + 0·2 „ „ . . .	0·006 „
1 „ „ + 0·4 „ „ . . .	0·02 „

TABLE XIV.

Hæmolysing doses in 1 mgrm. venom.	Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone 1666			
„ + 0·1 c.c. A.V.S. . 400	1266	10	126·6
„ + 0·2 „ „ . 166	233	10	23·3
„ + 0·4 „ „ . 50	116	20	5·8

TABLE XV.—*At* 35° C. *for six hours.*

Mgrms. of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.		
		0·1 c.c.	0·2 c.c.	0·4 c.c.
0·05	...	...	...	H.
0·04	...	...	...	„
0·03	...	...	...	„
0·025	...	...	...	„
0·02	...	...	H.	No H.
0·017	...	...	„	„
0·013	...	...	„	„
0·01	...	H.	„	„
0·008	...	„	„	„
0·006	H.	„	„	„
0·005	„	„	No H.	„
0·004	„	„	„	...
0·003	„	No H.	„	...
0·0025	No H.	H.	„	...
0·002	„	„	...	...
0·0017	„	„	...	...
0·0013	„	„	...	...
0·001	„	...	...	...
0·0008	„	...	...	...
Control saline	„	...	...	...

TABLE XVI.

	Minimal Hæmolysing dose.
Poison alone	0·003 mgrm.
1 mgrm. + 0·1 c.c. A.V.S.	0·004 „
1 „ + 0·2 „ „	0·006 „
1 „ + 0·4 „ „	0·025 „

TABLE XVII.

Hæmolysing doses in 1 mgrm. venom.		Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone . . .	333			
„ + 0·1 c.c. A.V.S.	250	83	10	8·3
„ + 0·2 „ „	166	96	10	9·6
„ + 0·4 „ „	40	126	20	6·3

TABLE XVIII.—*At* 35° C. *for twelve hours.*

Mgrms. of venom in 1 c.c.	Poison alone.	Quantity of serum added to 1 mgrm. venom.		
		0·1 c.c.	0·2 c.c.	0·4 c.c.
0·1	...	...	...	H.
0·08	...	...	...	„
0·06	...	...	H.	„
0·05	...	...	„	„
0·04	...	H.	„	„
0·03	...	„	„	„
0·025	H.	„	„	„
0·02	„	„	„	No H.
0·017	„	„	„	„
0·013	„	„	„	„
0·01	„	„	„	„
0·008	„	„	No H.	...
0·006	„	„	„	...
0·005	„	No H.	„	...
0·004	„	„	„	...
0·003	No H.	„	...	...
0·0025	„	„	...	...
0·002	„	...	...	...

TABLE XIX.

	Minimal Hæmolysing dose.
Poison alone	0·004 mgrm.
1 mgrm. poison + 0·1 c.c. A.V.S. . . .	0·006 „
1 „ „ + 0·2 c.c. „ . . .	0·00 „
1 „ „ + 0·4 c.c. „ . . .	0·025 „

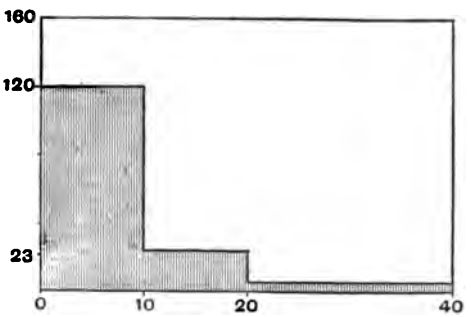
TABLE XX.

Hæmolysing doses in 1 mgrm. venom.	Difference.	Combining equivalents.	Hæmolysing doses per equivalent.
Poison alone . . . 250			
„ + 0·1 c.c. A.V.S. . 166·6	83	10	8·3
„ + 0·2 „ „ . 100	66	10	6·6
„ + 0·4 „ „ . 40	60	20	3·0

From these tables we see that one hour's exposure at 35° C. produces but little change in the minimal hæmolysing dose, which is now 0·0006. After six hours in the incubator, the

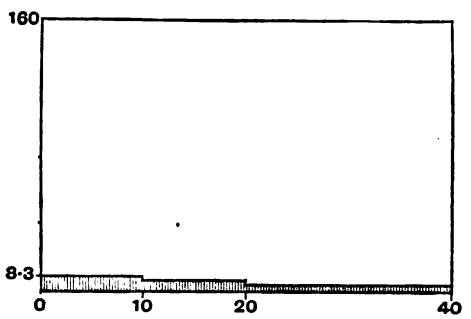
strength of the venom is reduced by four fifths, the minimal hæmolysing being now 0·003. Another six hours at this temperature produced but little or no change, the minimal hæmolysing dose being 0·004. The poison had after six hours apparently become stable, much as diphtheria poison does after a year at room temperature (Ehrlich).

The accompanying charts show these modifications graphically.

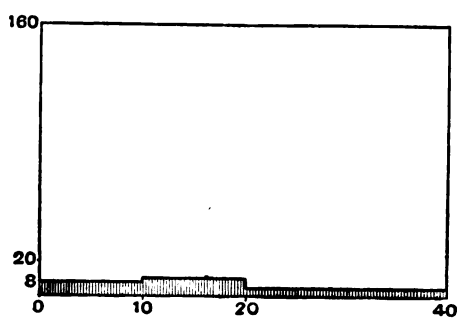


Neutralisation chart. (5) One hour at 35° C.

[The chart has been drawn for purposes of comparison with the scale of charts on p. 204.]



Neutralisation chart. (6) Six hours at 35° C.



Neutralisation chart. (7) Twelve hours at 35° C.

Objection may be raised to these experiments on the ground that the fluids used are all hypertonic. Now the hæmolytic action of cobra poison is diminished, and may even be abolished by hypertonic salt solution.[1] That the conclusions as to the neutralisation of cobralysin are not thereby invalidated is shown by the following considerations. The fluids most hypertonic were used in the neutralisation of 1 mgrm. of venom by the undiluted serum (L_o). In this case the amount of serum found is probably below the actual amount required for neutralisation in isotonic fluids. In diluting the mixture of serum and venom, the hypertonicity is diminished, so that when we are working with a hundredfold dilution of such a mixture the minimal hæmolysing doses are probably a little too high; but they will be more accurate than the estimation of L_o. In correcting these figures, then, we should obtain neutralisation charts similar to those already given, but their peculiar characters would be more pronounced. Undiluted serum was used for the estimation of L_o, in order to ensure as complete and rapid a reaction as possible, for which objects the higher the concentration of the reacting bodies the better.

Theoretical Considerations.

The charts which are figured in the preceding pages are merely graphic expressions of fact. They are, as I have described them, "neutralisation charts;" they assume no hypothesis beyond that which is now almost proved to be true by the large amount of indirect evidence brought forward on the subject, that the action between toxine and antitoxine is a direct one.

In interpreting these charts for any particular toxine, it is important to judge each toxine for itself, and only facts that have been ascertained for the toxine in question should be used for this purpose. The chaos of observations that existed before the appearance of the "Werthbemessung des Diphtherieheilserums" of Ehrlich was put into order by that paper; and there is, on this account, a danger of attempting to fit every toxine into the frame that was made by Ehrlich for diphtheria. An

[1] Stephens and Myers, 'Journ. Path. and Bact.,' Edinburgh and London, 1898, vol. v, p. 279.

impartial examination of every known toxine will probably throw much light on these questions.

Under the heading "Formation of Toxoids" the changes that this poison undergoes under various influences have been described. On looking over the tables, it will be noticed that the minimal hæmolysing doses, after one week in the cellar or one hour in the incubator, had risen. The minimal hæmolysing dose, when 0·1 c.c. serum was added to 1 mgrm. of venom, remained the same as with fresh poison. In other words, a substance has been formed which does not act on the blood-corpuscles, but which combines with the antitoxine. This substance is toxoid.[1]

Specificity of Toxoids.

In diphtheria poison, and in tetanolysin, the presence of toxoids has been demonstrated; and the question of the specificity of toxoids has an obvious bearing on the nature of these substances.

A diphtheria poison was therefore taken, which contained much toxoid, and the influence of this poison on the union of cobralysin and its antitoxine was determined.

The diphtheria poison[2] had a minimal lethal dose of 0·01 c.c. $L_o = 0{\cdot}57$ c.c.; $L+ = 0{\cdot}68$ c.c. The composition of this poison therefore was:

Toxine	57 equivalents
Toxone.	29·8 „
Toxoid	114 „

[1] Danysz ('Ann. de l'Inst. Pasteur,' Paris, 1899, tome xiii, p. 581) has recently attacked Ehrlich's hypothesis of the existence of toxoids. Taking a mixture of ammonia and sulphuric acid in the presence of sodium phosphate, he produced a curve of neutralisation similar to that given by Madsen for tetanolysin, and to those which are here drawn for cobralysin. He concludes that this peculiar curve is due to the presence of phosphates, but he does not specify the mode in which the phosphates are supposed to act. He gives so few details of his experiments that it is impossible to criticise them. It may be pointed out in this connection, that he worked with a fluid containing ammonia, sulphuric acid, sodium chloride, sodium phosphate (kind not stated); and it is quite impossible to say what chemical reactions take place in such a fluid. Possibly a toxoid in Ehrlich's sense is formed.

[2] I must here express my thanks to Dr. Cobbett for his kindness in placing this toxine at my disposal. The figures given as to its composition are from his notes.

The following mixtures were made:

A. 2 c.c. venom (=2 mgrms.) +1·2 c.c. diphth. toxine + 0·8 c.c. A.V. serum.
B. 2 „ „ „ +1·2 „ broth + 0·8 „ „
C. 2 „ „ „ +1·2 „ saline, 0·8% + 0·8 „ „

The estimation of the minimal hæmolysing dose gave the following result:

TABLE XXI.

	A.	B.	C.	Venom alone.
Minimal hæmolysing dose in mgrms. . . .	0·025	0·025	0·03	0·001

Here, then, the diphtheria toxine did not affect the neutralisation of the cobralysin; and, similarly, in the case of the neutralisation of 2 mgrms. of dry venom by 0·4 c.c. of antivenomous serum.

Another set of experiments was performed with tetanolysin and the above-mentioned diphtheria toxine. The following may be here quoted. The mixtures made were:

A. 1 c.c. tet. toxine (= 20 mgrms.) + 1 c.c. diphth. toxine + 1 c.c. A.T.S. $\frac{1}{1000}$
B. 1 „ „ „ + 1 „ broth + 1 „ „ „
C. 1 „ „ „ + 1 „ saline, 0·8% + 1 „ „ „

TABLE XXII.

	A.	B.	C.	Tetanus toxin alone.
Minimal hæmolysing dose in mgrms. . . .	0·5	0·5	1·0	0·05

The number of hæmolysing doses that have been neutralised is:

A 360
B 360
C 380

From this table it is evident that in the presence of the saline solution the neutralising power of the antitoxine was slightly greater than when broth or diphtheria toxine were present.

This difference is not great, though it was observed on several occasions. Bearing in mind, however, that in the diphtheria toxine there were contained 100 lethal doses and 200 equivalents of toxoid, and that the difference in the neutralising effect is only one of about 5 per cent., and is also shown by the control broth tube, we cannot ascribe it to the action of the diphtheria toxoids.

From these experiments we conclude that the toxoids of diphtheria do not affect the union of cobralysin or of tetanolysin with their respective antitoxines.

We have no knowledge to what extent the reaction of toxine and antitoxine is reversible; but it is reasonable to suppose that the compound formed by their union appreciably influences the reaction, tending to make it go in the opposite direction. In the presence of this compound, then, we should require more than the chemically equivalent amount of antitoxine to completely neutralise the toxine. We will suppose that 100 parts of toxine are equivalent to 100 parts of antitoxine. On mixing them, a state of equilibrium is reached in which we will suppose ninety parts toxine-antitoxine are present, ten parts of free toxine, and ten parts of free antitoxine.[1]

100 toxine + 100 antitoxine = 90 toxine-antitoxine + 10 toxine + 10 antitoxine.

In order to neutralise the ten parts of free toxine we must add more antitoxine; we will suppose that twenty parts more are necessary. To neutralise 100 parts of toxine, then, 120 parts of antitoxine are required.

Take the case now of a partial neutralisation. We have 100 parts of toxine, and we wish to neutralise ten parts of it. We add to it ten parts of antitoxine. Suppose a stage is reached in the reaction where nine parts of toxine-antitoxine are present, ninety-one parts of free toxine, and one of free antitoxine. Now

[1] In the above argument it has been assumed that the action of toxine on antitoxine results in the formation of a compound. It was indeed assumed, a few years ago, that their interaction resembled the formation of a double salt. Since the publication of Martin and Cherry's work, the experiments on which this view was founded have lost their significance. But even if a double decomposition between toxine and antitoxine occurs, the argument above is unaffected, for the products of the reaction would nevertheless tend to reverse it.

here clearly the system is not in equilibrium, as is seen by comparison with the former case.

100 toxine + 10 antitoxine = 9 toxine-antitoxine + 1 antitoxine + 91 toxine.

Here the reversing influence of the compound is less; for we have now a proportion of only nine of compound to ninety-one of free toxine, and one of antitoxine; whereas there the proportions were ninety of compound, but only ten each of toxine and antitoxine respectively. In this case, then, the large excess of free toxine would probably make the reaction complete, within our means of observation, because of the well-known effect of the presence in excess of either of two interacting substances. Ten parts of antitoxine have here neutralised ten parts of toxine. If we now add two more parts of antitoxine we have still a large excess of free toxine present, namely, ninety parts, which will neutralise the free antitoxine, yielding twelve parts toxine-antitoxine + eighty-eight parts free toxine. Thus, by adding one tenth of the antitoxine necessary for complete neutralisation, we have neutralised more than one tenth of the toxine; we have neutralised about one eighth.

We shall probably not err, then, in regarding the peculiar form of the neutralisation charts of cobralysin as due, in part at least, to this action of the compound of toxine and antitoxine. The amount of this factor is unknown, and we have, therefore, no means of exactly determining the quantity of toxoids actually present.

The form of the neutralisation chart depends on the relative amounts of toxine and toxoid, and on their relative affinities for the antitoxine. Were these both equal we should obtain a chart represented by a straight median line. Were there less toxoid than toxine present, with equal affinities we should obtain a chart of a curved line sinking from left to right. This supposition does not suffice for cobralysin, for, as we have seen, a toxoid makes its appearance very frequently on the extreme left of the curve, and we must therefore assume the existence of a toxoid with a greater affinity for the antitoxine than the toxine itself (prototoxoid). The frequent appearance of this prototoxoid is not proof that the toxine on the left of the chart is more unstable than, and different from, the rest of the toxine; it merely shows that the toxoid which is first formed is prototoxoid, that it has a greater affinity for the antitoxine than the toxine.

There is no evidence at present that the toxine of cobralysin consists of more than one substance,[1] and the facts can be explained by the simpler hypothesis that there is but one toxine, which decomposes first into a prototoxoid. On further changes, the prototoxoid breaks down into a substance having a less affinity for the antitoxine. At the same time more toxine has decomposed, forming more prototoxoid. In the fresh poison the charts indicate the presence of a toxoid with a less affinity for antitoxine than the toxine itself. But it should be pointed out that the form of the chart, after the poison has been for six or for twelve hours in the incubator, is explicable, on the supposition that here the toxoid has the same affinity as the toxine.

These conclusions have purposely been made indefinite, in order to draw from the facts above described for the cobralysin only those deductions which are warranted by them.

The venom used in these experiments was collected by the late Professor Kanthack. I wish here to express my indebtedness to Mr. Strangeways Pigg, in whose charge the stock was left, for his kindness in placing it at my disposal.

February 6th, 1900.

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24. *Preliminary note on cultures of streptotrichiæ from various sources.*

By C. Price Jones.

From the Bacteriological Laboratory, King's College, London.

These notes refer only to cultures made on agar, beef-broth, blood-serum, gelatine, and potato. As yet no inoculations of animals have been made.

Three examples of the streptothrix group were under observation, obtained respectively from horse-dung, from water, and from sound—*i. e.* not "faulty"—rum.

All three show strong relationship to each other but seem in many ways to be distinct from varieties hitherto described.

They each exist as branched threads arranged in a network. The threads at first show no beading, later become beaded, and later still, especially on potato, break up into spirilliform and

[1] With the question of the existence of a toxine, and its behaviour to the red corpuscles, I hope to deal in a later paper.

curved non-motile segments, and discharge the beads as free varying-sized spores, the curved forms and spores growing into long threads when transplanted into fresh medium.

No true coccal forms nor motile bacillary forms appeared in any of the cultures.

Streptothrix from horse-dung.

On *agar*.—Varying sized discs; buff-coloured, tough, firmly planted, smooth and flat at first, wrinkled and limpet-like later. At times a chalky efflorescence appears later.

Microscopically.—Network of long threads, beaded and non-beaded with branches of varying lengths. At times a few free spores.

In *broth*.—Flocculent colourless growth at bottom of tube, broth remaining clear.

Microscopically.—Indistinguishable from growth on agar.

On *solid blood-serum*.—Irregular, raised, wrinkled growth, tough, and firmly planted; of red-brown or pale colour of medium, which is rapidly liquefied. On one occasion liquefaction was delayed for two weeks, and was then only slight.

Microscopically.—Threads mostly non-beaded; some are beaded, but there are no free spores.

On *gelatine*.—Growth appears after five to fourteen days slow, and after many weeks only slight—a compact irregular mass, sinking gradually in a cupped depression into the medium. There is no cloudiness or coloration of the gelatine. Liquefaction varies. On several occasions, after a week, many small disc-like growths appeared on the surface and in the depth of the gelatine, and in about a month liquefaction was complete; but mostly only a cupped depression, and no true liquefaction, occurred.

Microscopically.—Beaded, but mostly non-beaded threads; sometimes a few spores.

On *potato*.—In from three to seven days a raised chalky coral-like growth. After about fourteen days a grey margin developed on several occasions round the base of the chalky mass. No coloration of the potato.

Microscopically.—Beaded threads, some spirilliform, and others breaking into curved forms; also many free spores, especially in the grey margin.

Remarks.—Sub-cultures very difficult to obtain; on agar about 50 per cent., in broth about 75 per cent., on gelatine less than 40 per cent., and on potato only about 20 per cent. For many weeks—over two months—no sub-cultures grew.

Streptothrix from water.

On *agar.*—Varying sized discs; pale buff colour; tough, firmly planted; at first smooth and flat, later often efflorescence.

Microscopically.—Network of long threads, non-beaded and beaded with branches of varying lengths; at times a few spores.

In *broth.*—Flocculent, colourless growth at bottom of tube, broth remaining clear.

Microscopically.—Indistinguishable from growth on agar.

On *blood-serum.*—Varying sized growth, slightly raised, tough, and firmly planted; pale colour of medium; liquefaction slow.

Microscopically.—Beaded and non-beaded threads; no spores.

On *gelatine.*—Growth after fourteen days. Only once in ten trials. Slow, and after many weeks only slight. A compact irregular mass, sinking gradually in a cupped depression into the medium. No cloudiness.

On *potato.*—In forty-eight hours growth appears, buff-coloured, raised, wrinkled, and hard; being gritty to the needle. Chalky efflorescence occurs only occasionally. In one culture a grey ashy powder was deposited on the chalky surface, and later the entire growth became black and dried up.

Microscopically.—Beaded and non-beaded threads stouter than those from agar or broth, often ending in wider non-staining portions; also free varying-sized spores. The grey powder consisted of spores and spirilliform threads, with beads (spores) bulging the threads; also threads broken into curved forms.

In a large proportion of sub-culturings no growth could be obtained on any medium, especially on gelatine and potato.

Streptothrix from rum.

On *agar.*—Varying sized discs, pale buff colour, tough, and firmly planted; at first smooth and flat, later limpet-like. No chalky efflorescence in any sub-culture yet made.

Microscopically.—Network of long threads, non-beaded and beaded, with branches of varying lengths. No free spores, but some threads end in oval swellings.

In *broth.*—Flocculent colourless growth at bottom of tube; broth clear.

Microscopically.—Indistinguishable from growth on agar.

On *blood-serum.*—Rapid growth in twenty-four hours. At first pale buff, tough, and firmly planted discs; later bulging and much raised, with smooth shining surface of orange tint. Slight liquefaction in ten days.

Microscopically.—Non-beaded and beaded threads; no free spores.

On *gelatine.*—Slight but marked growth in five days to a week. At first an irregular mass; later showing many small discs of cream colour projecting into the medium; very tough. Tendency to depress the surface, but no definite liquefaction. After from ten to fourteen days the medium is clouded.

Microscopically.—Non-beaded and beaded threads; no free spores; no oval swellings at ends of threads.

On *potato.*—In twenty-four hours a buff-coloured growth, raised, wrinkled, and hard. In from twenty-four hours to a week part or whole has become chalky and coral-like. Later a grey ashy powder is deposited on the chalky surface, which is black when disturbed with a needle; and later the whole growth resembles a cinder.

Microscopically.—Early growth shows beaded threads, later stouter threads, especially the lateral branches, which are often unstained, or only faintly so. Many free oval spores. The grey powder shows oval spores, and some threads breaking up into curved segments.

Sub-cultures of grey powder (spores) on agar, broth, and blood-serum show only threads, mostly non-beaded; sub-cultures on gelatine, a spreading growth, indenting the surface and showing threads, mostly non-beaded, with many short branches; also spores growing out into threads. All sub-cultures grew readily. *May 1st*, 1900.

25. *Thyroid of puppy of thyroidless bitch.*

By W. Edmunds.

From the Laboratory of the Brown Institution.

(With Pl. VIII, figs. 4, 5.)

In 1896 Halsted announced that he had found that the thyroid glands of the new-born pups of dogs whose thyroid lobes had been in part excised were hypertrophied. The thyroid glands of these puppies he found were about twenty times as large as normal; microscopically there was an entire absence of colloid, and only rarely a trace of a vesicle.

These experiments I have repeated. From a bitch there were removed on one side the thyroid lobe together with the parathyroids, and on the other side nearly the whole of the thyroid lobe, but leaving one parathyroid and a morsel of thyroid attached.

About four months later the bitch gave birth to a puppy. The puppy was killed and the thyroid dissected out; it seemed to me large. On microscopic examination there was found an entire absence of colloid, and the secreting cells lining the vesicles were much taller than normal.

The above changes are those found in compensating hypertrophy of the thyroid, and are presumably due to an hypertrophy of the thyroid of the unborn puppy to compensate for the maternal deficiency.

It may here be remarked that the health of women suffering from either myxœdema or Graves's disease is said to be much improved during pregnancy.

References.

Halsted.—'Johns Hopkins Hospital Reports,' vol. i, 1896.
Charcot.—'Gazette Hebdomadaire,' vol. ix, 1862, p. 562.

May 29th, 1900.

26. *Fibro-myxoma of sympathetic ganglia.*

By H. Morley Fletcher.

(With Pl. VIII, figs. 1, 2.)

This specimen was obtained from the body of a woman aged 32, who was admitted on January 9th, 1900, to St. Bartholomew's Hospital under Dr. Hensley's care, suffering from anæmia. In September, 1898, she suffered from pain in both groins, which was worse on walking, and in consequence had not left her bed since October. In November she felt sharp pain in the left side of the chest. The pains in the chest continued, and she grew gradually weaker and paler. On admission she was found to be very anæmic, but fairly well nourished. There was impairment to percussion, weak breathing, and pleural friction at the left base. No nervous symptoms were noticed during the course of her illness. Examination of the blood gave:

Red corpuscles . .	1,300,000 per c.mm.
Leucocytes . . .	5000 „ „
Hæmoglobin . . .	23 per cent.

The red corpuscles were of irregular size and shape. The case was regarded as probably one of pernicious anæmia with pleurisy. She died on February 22nd, and the *post-mortem* examination made by Dr. A. E. Garrod revealed a large tumour in the posterior mediastinum. The pleuræ were half filled with fluid. The liver was studded throughout with small nodules of secondary new growth, none larger than a pea. A small nodule was also found on the surface of the upper lobe of the right lung. The tumour, with the portion of the spinal column to which it was connected, was hardened in formalin *en masse*.

Naked-eye appearances.—The tumour forms a large bilobed mass, measuring 6½ inches vertically, and 6 inches horizontally. It lies on the bodies of the dorsal vertebræ, extending from the 6th to the 11th. The left lobe is considerably the larger. The two lobes embrace the thoracic aorta, but do not compress it. The surface is smooth and covered by the pleura. These large masses are composed of a pale, somewhat gelatinous-looking

substance, having a firm, elastic consistence. On the left side a mass of dark, hæmorrhagic growth is seen lying in front of portions of the 7th, 8th and 9th ribs, which are here invaded by the growth, as are likewise the corresponding intercostal muscles. The spinal canal has been laid open and shows a thin sheet of pale growth similar to that composing the large bilobed tumour, extending for a distance of 4 inches outside the dura mater, apparently without involving it. The spinal cord is natural. On examining the cut surfaces of the bodies of the vertebræ, they are seen to be infiltrated with pale growth. I am unable to state to what further extent the spine may have been involved, as the rest of the column was not examined.

Microscopical examination. — The pale, gelatinous-looking growth forming the bilobed tumour is composed chiefly of myxomatous tissue containing a large number of delicate fibres scattered throughout it. In places these fibres are arranged in bundles; they resemble non-medullated nerve-fibres, but most are probably connective tissue. Here and there in sections from this part of the growth are found scattered large round cells with a distinct nucleus and nucleolus resembling sympathetic nerve-cells. In other parts there are groups of similar but somewhat smaller cells. These cells are similar to those occurring in a large round-celled sarcoma. The hæmorrhagic part lying under the ribs is definitely sarcomatous. Here the growth is composed of small spindle-cells, and is very vascular. The growth in the bodies of the vertebræ and the secondary nodules in the liver exhibit the same kind of cells last-named, as does also the growth in the muscles.

The shell of pale growth in the spinal canal differs considerably from this. It contains small nerves, much fibrous tissue and fat, the latter probably the remains of that normally found in this situation. There are also some small spindle- and round-cells, but the most interesting point lies in the existence of groups of large round cells, which suggest sympathetic nerve-cells, and resemble the cells found in the bilobed tumour. The spinal cord exhibits no morbid change.

When we consider the histological characters of the large tumour of the posterior mediastinum, we are drawn to the conclusion that it is most probably a fibro-myxoma which has arisen in connection with one or more of the thoracic sympathetic

ganglia. The primary mediastinal tumour has evidently become sarcomatous, and has given rise to the small spindle-celled growth found in the ribs, vertebral bodies, and the liver. The shell of growth lying in the spinal canal outside the dura mater is probably a direct extension of the main mass of the primary growth through the spinal foramina. It is improbable that the main tumour is a true neuroma of the sympathetic system. The nerve-cells, though numerous, are not present in sufficient quantity, and it is doubtful whether non-medullated nerve-fibres are present. True neuromata (neuroma ganglio-cellulare sympathicum) are recorded by Borst,[1] Busse,[2] Laurez,[3] and others, and like all tumours connected with the sympathetic ganglia are of very great rarity.

There can be no question in this case that the tumour is not primarily a sarcoma of the sympathetic ganglia. The sarcomatous portion is very small and localised, and differs entirely in structure from the main mass.

It might be suggested that the thoracic tumour has no connection with the sarcomatous growth in the bones, which has arisen independently and subsequently invaded it. This would be difficult to disprove, but such coincidence is highly improbable, and is opposed to the well-established fact that neuro-fibromata not infrequently become sarcomatous. *May 29th*, 1900.

Report of the Committee on Morbid Growths on Dr. H. Morley Fletcher's specimen of tumour of the posterior mediastinum.—We have carefully examined the sections submitted to us by Dr. Fletcher, and have little either to add to the author's histological description, or to object to in his main conclusions.

Mediastinal tumour.—The fasciculi in this, though at first suggestive of non-medullated nerve, we regard as connective tissue, for the following reasons:—the elongated nuclei and the fibre are in many instances wanting in parallelism; the amount of fibrillated material intervening between the nuclei is of irregular and often wide extent; the strands of fibre intersect in a more complex manner than would be the case with nerve. The

[1] *Borst*, 'Berlin. klin. Wochenschrift,' 1897, s. 1063.
[2] *Busse*, 'Virchow's Arch.,' Bd. cli, supplement, s. 66, 1898.
[3] *Laurez*, 'Virchow's Arch.,' Bd. xlix, s. 435, 1870.

looser areas of the growth pass imperceptibly into others where the tissue is more compact and obviously of the connective kind, arranged in intersecting bundles with parallel elongated nuclei; the separation of the bundles is, in our opinion, evidence of an œdematous condition such as is not uncommon in tumours of this class: the presence of "mucous tissue" supports such a view. The strands of fibre frequently suggest tubular structures, but after prolonged study we have come to the conclusion that the appearances result from the dissociation of delicate fibres and lamellæ of corrective tissue, for similar appearances occur concentrically about minute vessels; and elsewhere when traced to their termination the apparent tubules frequently dilate and become lost in a widely open mesh of fibre and film.

It is otherwise with certain groups of cells present in sections of the mediastinal tumour; these we have no hesitation in classing as nerve-cells. They have a large, spherical, vesicular nucleus (sometimes two) with a strikingly conspicuous nucleolus; the cell-body is finely granular, and, in some, contains pigment; it takes, as a whole, a deeper stain than that of the connective tissue elements (eosin).

The growth around the spinal cord.—This likewise presents groups of polyhedral cells, like those just described. In this growth there are, as the author observes, a certain number of fat cells, and in addition, the preparations exhibit cross sections of definite fasciculi of medullated nerves. The latter are obviously spinal nerves involved in the tumour on the outer aspect of the dura mater; the presence of fat cells in their neighbourhood accords with such a view, these cells being unquestionably elements of the adipose tissue surrounding the spinal theca.

The growth in the liver is an ordinary spindle-celled sarcoma; nor do those in the bodies of the vertebræ or in the muscle present any unusual characters.

The nerve cells in the main mediastinal growth we regard as sympathetic cells involved in it: those in the perithecal extension are possibly of the same class, or they may pertain to ganglia on posterior nerve roots. The last-named possibility is suggested by their contiguity to fat cells, by their very close grouping, by the presence of fasciculi of medullated nerves in their immediate proximity, but especially by the presence of what are undoubtedly medullated nerve-fibres with distinct axis

cylinders, between the nerve-cells themselves. The preparations do not allow of any minute observations upon the capsules and spaces about the last-named elements. We think the exhibitor has properly classed the primary growth as a fibro-myxoma, since we do not regard the presence of nerve-structures as an integral feature in the new formation.

(Signed) R. G. Hebb.
S. G. Shattock.

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27. *Two cases of congenital sacro-coccygeal tumour, one of which developed carcinomatous characters.*

By H. Morley Fletcher and H. J. Waring.

Congenital tumours in the sacro-coccygeal region, which take their origin in the remains of the post-anal gut, or of the neurenteric canal, according to most authorities have not had malignant characteristics; in fact, so far as we can ascertain such a condition is extremely rare. The first of the two specimens which we are recording exhibited marked malignancy; the second, though similar in many respects to the first, presented none of these characteristics, although histologically it closely resembled it.

The first specimen is a sacro-coccygeal tumour removed by Mr. Langton from a male child, and the pelvis from the same child, who died three and a half months later from recurrence in the lumbar and inguinal lymphatic glands. The history of the case is as follows:—The child when admitted to St. Bartholomew's Hospital was two years old. It had a large sacro-coccygeal tumour about three inches in diameter, projecting backwards from the sacral region, more on the left side than on the right. The tumour had existed from birth, and had been increasing in size. It was painless, and could be moved about to a considerable extent; it could be felt, *per rectum*, projecting into the pelvis, pushing the rectum forwards. The coccyx was removed with the whole of the tumour. The child made a good recovery from the operation, but was readmitted to the hospital two months later with extensive recurrence of the growth within the pelvis, which proved fatal in less than three and a half

DESCRIPTION OF PLATE VIII.

Illustrating Dr. H. M. Fletcher's communication (p. 222); Dr. F. P. Weber's communication (p. 233); and Mr. W. Edmunds's communication. (Page 221.)

Figs. 1, 2, illustrating Dr. H. M. Fletcher's specimen of Fibro-myxoma of Sympathetic Ganglia. (Page 222.)

FIG. 1.—A section of the extension of the growth within the spinal canal, showing spindle-cells and groups of nerve-cells.

FIG. 2.—A section of the mediastinal growth, showing loosely connected strands of fibrillated tissue, and a certain number of nerve-cells.

(From drawings by Danielsson.)

Fig. 3, illustrating Dr. F. P. Weber's case of a peculiar form of Cirrhosis of the Liver. (Page 233.)

The section shows the centro-acinous distribution of the fibrous tissue. The least altered hepatic cells are situated chiefly at the periphery of the acini, and are grouped around the portal vessels, the lumina of which are apparent in the preparation.

(From a drawing by Danielsson.)

Figs. 4, 5, illustrating Mr. W. Edmunds's note on the Thyroid of the Pup of a Thyroidless Bitch. (Page 221.)

FIG. 4.—A section of the thyroid described. There is a complete absence of colloid; the cells lining the acini are taller than normal. (× 220.)

FIG. 5.—A section of the thyroid of a healthy new-born pup, showing the amount of colloid present. (× 220.)

(From drawings by M. H. Lapidge.)

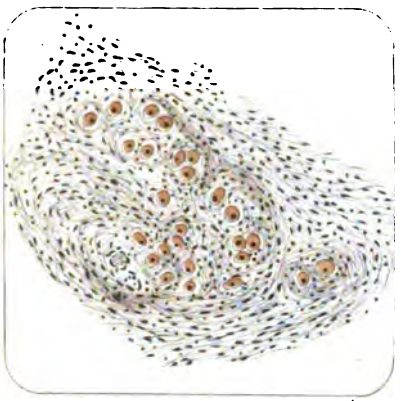

Fig. 1.

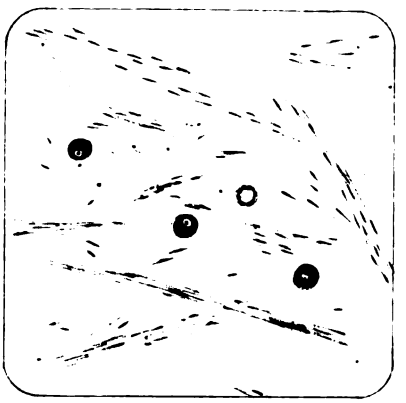

Fig. 2

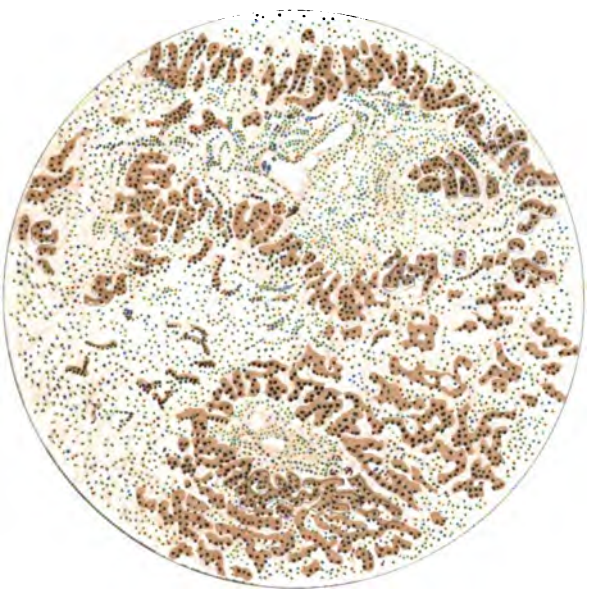

Fig. 3.

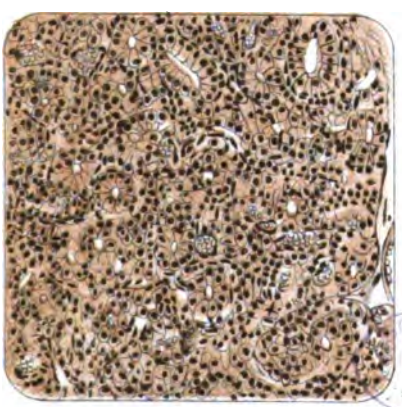

Fig. 4.

Fig. 5.

months after the operation. We would take this opportunity for thanking Mr. Langton for his kind permission to publish the case.

The tumour which was removed is partly cystic and partly solid, and lies immediately beneath the skin, which however is not involved. One portion is dense and firm, being composed chiefly of fibrous tissue; this portion showed several smooth-walled cysts of various sizes, which in the fresh state contained a clear, glairy fluid. The rest of the tumour is of a soft brain-like consistency, and the seat of numerous small hæmorrhages.

Microscopical examination.—The cysts are lined by columnar epithelium; they lie in a vascular connective tissue, which is myxomatous in places. The soft, solid portion of the tumour shows the structure of an adeno-carcinoma.

At the *post-mortem* examination the pelvis and viscera were removed as a whole. In the specimen now shown the right os innominatum has been removed, so as to expose the pelvic contents. The pelvis is largely occupied by a mass of recurrent growth which has pushed the sacrum backwards, and has enveloped without actually invading the rectum. At the pelvic brim the rectum is somewhat narrowed, and above this the gut is greatly distended. The bladder is not involved. The iliac and lumbar glands on the left side form masses equal in size to the left kidney; stretched across these masses and much dilated is seen the left ureter as a ribbon-like band. The left kidney, which is smaller than the right, is in a condition of early hydronephrosis. The right kidney shows no distension of the pelvis or calices. No metastatic growths were found in any of the viscera.

Microscopically the growth in the glands is an adeno-carcinoma identical with the primary tumour.

The second specimen was taken from the body of a female infant, who died seven days after birth. Labour was normal, except that the tumour gave trouble in passing over the perinæum. There was no other congenital defect in the body.

The preparation exhibited is a median vertical section through the lower part of the body, and shows a large sacro-coccygeal tumour *in situ*. The sacrum and coccyx are pushed back by the growth, which appears to have originated between them and the rectum. The rectum is in its usual position, lying

entirely in front of the growth. The tumour is encapsuled, and shows no sign of infiltrating the adjacent structures. It forms a globular mass, three inches in diameter, protruding backwards towards the nates. It is cystic, some of the cysts being of considerable size, and in most of the more solid portions of the growth numbers of minute cysts can be seen. The cavities of the large cysts are in part occupied by soft intra-cystic growths. In the fresh condition the cysts contained glairy, mucoid fluid.

Microscopical examination.—The cysts are lined with columnar-celled epithelium, for the greater part in a single layer. In some places, however, this lining can be seen to consist of a squamous, stratified epithelium. Intra-cystic growths are abundant, and are to be seen in every stage of development. The tumour as a whole may be regarded as an adeno-cystoma. But in the more solid parts, where no epithelial elements are present, the growth consists of embryonal connective tissue, partly myxomatous, partly cellular, resembling a sarcoma, and small islands of hyaline cartilage occur in it here and there.

The extent of our knowledge as to the origin of sacro-coccygeal tumours is undoubtedly unsatisfactory. Tumours arising in this situation, and consisting in the main of epithelial elements, may be derived from—

(*a*) Fœtal inclusions or dermoid cysts.

(*b*) The coccygeal or Luschka's gland.

(*c*) The remains of the post-anal gut.

(*d*) The neurenteric canal.

(*a*) *Fœtal inclusions.*—This is highly improbable, as the epithelium is columnar in character and there is a total absence of any epidermal structures.

(*b*) *The coccygeal or Luschka's gland.*—This gland normally contains a basis of fibrous and vascular tissues, in which are embedded masses of epithelial cells, each cell being polyhedral in shape. We do not regard either of the two cases which we have described as originating in this gland, on account of the different character of their epithelial elements. It is interesting to note that in a case of sacro-coccygeal tumour described by Schmidt the coccygeal gland was found lying intact by the side of the tumour ('Archiv für path. Anat. und Phys.,' 1888, Bd. cxii, S. 3).

(*c*) *Remains of the post-anal gut.*—We regard this as the

most probable origin of the first of these tumours. The columnar character of the epithelium and the anatomical position of the tumour both indicate this as the most likely hypothesis. This view is further supported by the fact, that the malignant portions of the tumour first described are identical in structure in most respects with that found in carcinomatous growths of the rectum.

This view as to the origin of sacro-coccygeal tumours is held by Mr. Bland-Sutton. We would venture to suggest, however, that the term "thyro-dermoids," which he has applied to similar growths, is one which is not applicable to this class of tumours, and is, moreover, distinctly misleading.

(*d*) *Neurenteric canal.*—This we consider to be the most likely seat of origin of the tumour in the second case recorded. Histological investigation of the tumour has shown that it contains—cysts lined with epithelium, which in some places is columnar in type and in others is of the stratified squamous variety, localised masses of hyaline cartilage, and a quantity of tissue, mesoblastic in origin, which has the structure of cellular embryonic tissue, and resembles in many respects the tissue found in a mixed-celled sarcoma. The neurenteric canal in the young fœtus forms a communication between the posterior portion of the alimentary canal and the terminal extremity of the primitive nervous groove or canal, and lies in close connection with the caudal extremity of the notochord. This canal is lined internally by columnar-celled epithelium on the alimentary side, and with epithelium of a more squamous type on the medullary side.

Taking into consideration these points in connection with the histological structure of the tumour and the neurenteric canal, it appears to us that this explanation of the pathology of the second tumour is the most likely hypothesis.

Malignancy.—The malignant characters of the first tumour, its resemblance in structure to a columnar-celled carcinoma of the rectum, and the secondary growths in the lumbar lymphatic glands, are points of unusual interest. Few cases appear to be on record in which a columnar-celled carcinoma has been met with in a child of two years of age. *May 29th*, 1900.

28. *A case of megalencephaly.*

By H. Morley Fletcher.

This brain was taken from the body of a boy aged ten, who was in St. Bartholomew's Hospital under the care of Sir Dyce Duckworth, and died of pericarditis and endocarditis after a very short illness. He was noticed to have a large head, but nothing was then known as to his past history; since his death I have succeeded in tracing his parents and have learnt the following facts. The labour was a normal one, but since birth his head was noticed to be of unusual size, so that when an infant he appeared to have difficulty in supporting it, and later, at school, was known as "big head." His growth was normal, and there was no history of injury. As regards his mental power his parents described him as a backward boy, neither specially stupid nor specially bright, and he was just able to read. He suffered from frequent headaches, but never had fits or vomiting. The special senses were normal. The father, a window-cleaner, was a man of average intelligence. His head was of somewhat unusual size, chiefly due to an increase in the frontal region, resembling that seen in a rachitic infant. The only other child, an adult daughter, was said to be normal in all respects. No evidence of congenital syphilis could be obtained.

The *post-mortem* examination was made by Dr. Calvert sixteen and a half hours after death. Except for the condition of the head nothing need be mentioned. The skull-cap was natural except for its size, and exhibited no marked thinning. The membranes were normal also. The brain weighed 73 oz., its substance was firm and dense in the fresh condition. It was hardened in formalin, and is now mounted in glycerin. It is obviously of enormous size. The increase in bulk is uniform, the different parts of the brain retaining their relative proportions. The vessels and pia mater are natural. The convolutions are well formed, and present no abnormalities of shape or number. An incision into the ventricles showed that they were in no way distended. The texture of the brain substance, both

white and grey, is dense and firm, but presents no change to the naked eye. The spinal cord was not examined.

Microscopically, the chief change appears to be a great increase in the amount and density of the neuroglia, both of the grey and of the white matter. The nerve-cells in the grey matter show no marked alteration in size or number, nor any definite degeneration. I must here offer my thanks to Dr. Batten for his kind help in the microscopical examination.

In certain of the sections of the cortex stained with hæmalum or alum-carmine I found very numerous non-nucleated round bodies, more abundant in the white matter than in the grey, which stained a pale blue colour with hæmalum, and pink with alum- or borax-carmine. These bodies were not present in paraffin sections unless passed very rapidly through the various reagents. They were not found in celloidin preparations, but were most conspicuous in frozen sections. They were also present in sections of the medulla. Prolonged treatment with alcohol or xylol appeared to dissolve them out, leaving distinct spaces where they had previously been. Acids and alkalies had no action on them. They did not give the reactions of cholesterin, and they are not corpora amylacea. As to their nature I can only hazard the opinion that they are composed of some fatty substance. It is possible they may be in some way due to the method of preparation, and I therefore refer to them with considerable diffidence. They occur, however, in such large numbers that they may possibly have some relation to the enormous increase in size and weight of the brain.

There can be little doubt that this condition corresponds with that generally known as *hypertrophy of the brain*, of which many cases have been described, but none, I believe, shown at this Society. The case is of additional interest since I believe it to be the heaviest brain recorded, as it weighed 73 oz., or 2065·9 grms. This is considerably in excess of the well-authenticated weights of the largest normal adult brains.

Boyd[1] gives the weight of the normal male brain between seven and fourteen years as 1301 grms. (46 oz.). Pfister[2] gives it as 1280 grms. (45·2 oz.) between nine and fourteen years.

The term *hypertrophy* has been applied to the large brains

[1] Boyd, 'Phil. Trans.,' 1860.

[2] Pfister, 'Arch. f. Kinderheilkunde,' 1897, Bd. xxiii, p. 164.

found both in children and adults, most of which have exhibited some degree at least of mental deficiency. Virchow stated that the cause of the enlargement was an increase in the neuroglia, and many observers have adopted this view.

If it be true that we have to deal in these cases with some pathological change in the tissue, which leads to a diminution in functional activity, the term hypertrophy is certainly misapplied, as it should be employed only to imply increase in bulk of a normal tissue when associated with increase of function. It would be preferable, on this account, to use the term "*megalencephaly*," suggested by my friend Dr. Andrewes, as more accurately defining this form of enlarged brain.

There can be little doubt that the large brains found in backward children or in lunatics, as recorded by Middlemas,[1] Grant,[2] and others, have no connection with those of great weight found in certain individuals characterised by their intellectual power. Several of these distinguished persons have possessed a type of face suggesting an early hydrocephalus, and in connection with this Perls has suggested that the normal pressure exerted on the brain by the skull, is reduced in cases of hydrocephalus which are undergoing cure. In such circumstances the brain may grow abnormally in proportion to the increased capacity of the skull. Edinger[3] lends further support to this view.

The rarest forms of so-called hypertrophy are those in which the increase in bulk is limited, as in the interesting case of partial hypertrophy described by Tuke[4] where the change was unilateral.

In conclusion, I would offer to Sir Dyce Duckworth my thanks for permitting me to publish this case.

May 29th, 1900.

[1] Middlemas, 'Lancet,' 1895, vol. i, p. 1432.

[2] Grant, 'Lancet,' 1895, vol. ii, p. 149.

[3] 'Anat. of Central Nervous System in Man and Vertebrata,' translation by Hall, 1899, p. 206.

[4] Tuke, 'Journal of Anatomy and Physiology, 1873, pp. 257—266.

29. *A peculiar form of cirrhosis of the liver.*

By F. Parkes Weber.

(With Pl. VIII, fig. 3.)

The patient, Mrs. L—, aged 62, began to lose weight about the end of 1898. She had previously been a strong woman, and there was nothing special to note in the past history. There was no evidence of syphilis. The symptoms accompanying the emaciation were anorexia (with a feeling of nausea, but without actual vomiting), and great debility with extreme breathlessness on exertion. She was at first somewhat improved by an almost exclusively milk diet and by a bitter medicine containing arsenic. In February, 1899, the liver and spleen were both felt enlarged and hard below the ribs, but no definite tumour could be made out, though the presence of some abdominal malignant disease was suspected. The pulse was frequent, and there was dyspnœa on the least exertion, but nothing special was made out by physical examination of the thoracic organs, except a few crepitations in the left subscapular region. The urine (sp. gr. 1010) was clear and pale, free from sugar, but containing a trace of albumen. The patient lost ground slowly. The anorexia continued and the emaciation progressed somewhat, but no distinct tumour could be detected in the abdomen. There was pigmentation of the skin, which might, however, be partly caused by the arsenic taken as a medicine. Occasionally the patient, a woman of great energy, appeared to improve slightly in some respects. Supra-renal gland substance was at one time tried as a medicine, but with no decided effect. The dyspnœa on exertion increased, and it was accompanied by a marked tendency to cyanosis, much irritating cough, and (mucous ?) expectoration, sometimes streaked with blood. The finger-tips became "clubbed," and there was crepitation at the base of both lungs (chiefly left side). A slight rise of temperature (under 100° F.) was sometimes noted in the evenings. On 14th November, 1899, the patient became rather suddenly partially unconscious. The loss of consciousness afterwards became more marked, and death took place on 18th November.

A *post-mortem* examination of the abdomen was permitted. The omentum and mesentery were fairly well supplied with fat in spite of the emaciation. No malignant tumour could be found. The spleen and liver were enlarged, and there were some small stones in the gall-bladder. The kidneys appeared normal. The pancreas felt hard in parts, but no signs of new growth could be detected. There were some enlarged lymph-glands in the neighbourhood of the hilum of the spleen, and near the pancreas. The stomach, pylorus, and intestines appeared normal. A portion of the liver close to a spot where the capsule was thickened was removed for microscopic examination, as well as portions of both supra-renal capsules, the pancreas, and the enlarged lymphatic glands.

Microscopical examination of the supra-renal capsules showed nothing noteworthy, excepting a certain amount of pigmentary change of the cortical substance. The sections of the pancreas were not very satisfactory, but showed nothing remarkable. The sections of lymphatic gland showed hyperplasia and some fibrotic change; sections stained for tubercle bacilli gave a negative result. It is to the changes in the liver that I wish to draw special attention.

The sections of the liver gave evidence of passive congestion and of slight chronic periportal inflammatory changes. At one part, however, there was a diffuse fibroid change reminding me very much of the diffuse changes sometimes met with over the whole liver in children with congenital syphilis, and with the similar changes met with over larger or smaller areas of the liver in some syphilitic adults. The possibility that the change might be of a syphilitic nature was increased by the fact that in some places the central parts of the lobules were most involved in the fibrous process, whilst the hepatic cells were least affected around the portal vessel at the periphery of the lobules. Last year I drew attention to the tendency towards this "centro-acinous" distribution of the fibroid process as a characteristic of certain diffuse syphilitic changes in the liver ('Trans. Path. Soc. Lond.,' vol. l, p. 142), and pointed out that in such cases "the fibrous change is generally most advanced in the central portions of the acini, and least noticeable around the portal vessels. In fact, the change is quite distinct from that of all ordinary cases of cirrhosis, in that the best-preserved liver cells

are those at the periphery of the acini, precisely those which are most likely to be encroached upon in ordinary cirrhosis." I thought this might possibly be pathognomic of the process being syphilitic, but I find that Dr. E. L. Opie ('Journal of Experimental Medicine,' New York, 1899, vol. iv, p. 279) calls attention to a somewhat similar distribution of the fibrous process in the liver of his "Case of Hæmochromatosis." His exact words are:—"There is but little invasion of the periphery of the lobule by fibrous strands, but surrounding the central vein a mass of tissue penetrates the lobule and sends out irregular, radiating projections along the capillaries between the columns of liver cells." Dr. Opie's remarks on the liver in his case of hæmochromatosis are interesting in regard to the present case, when it is remembered that pigmentation of the skin was a prominent symptom during life in both cases. In the present case, however, other pathological features of hæmochromatosis were absent, and no glycosuria was noted during life. In regard to the question of syphilis, it may be mentioned that sections of the liver and lymph-gland stained with methyl violet gave no indication of any lardaceous change. On the whole, however, I am inclined to think that the condition is syphilitic in nature, and I doubt whether the same diffuse fibrotic changes in the liver are met with in any other disease, for Dr. Opie's description of the centro-acinous changes in his case does not quite correspond to the changes in the present case.

As there were no illustrations in my previous paper, I this time give a figure to show what I mean by the tendency to "centro-acinous distribution of the fibrous process" in these cases. It is drawn from a section of the liver in my previous case ('Trans. Path. Soc.,' vol. l, p. 142), and shows two portal vessels with the adjoining portions of the hepatic acini. It will be seen that the least altered hepatic cells are chiefly situated at the periphery of the acini and are grouped around the portal vessels; in the central portions of the acini the fibrous change is much more advanced, the glandular cells of the liver being more or less completely replaced by fibrous tissue.

May 29th, 1900.

30. *Furrowed and constricted liver from a case of chronic pulmonary emphysema.*

By F. Parkes Weber.

The liver (weight 52 oz.) shows a broad constriction, about 3 cm. in breadth (at the constriction the hepatic capsule is increased to the thickness of 1 mm.), extending transversely across the lower part of the anterior surface, and corresponding with constrictions produced by "tight lacing." The mid horizontal line of this constriction is about 4 cm. from the lower border of the right lobe. In the upper part of the right lobe, above the band of constriction and nearly at right angles to it, is a deep furrow (2 cm. in depth at its deepest part), which, during life, corresponded in position to one of the ribs, and probably likewise to a fold or projecting ridge of the diaphragm.

The liver in the present case is from a man, F. S—, aged 62, affected with emphysema of the lungs, and who died (January, 1900) from purulent pericarditis.

Professor E. Ziegler ('Special Pathological Anatomy,' translated by MacAlister and Cattell from the eighth German edition, London, 1897, p. 697) says:—"The outer surface of the right lobe is frequently marked with shallow grooves corresponding to the course of the ribs. Oftener still the upper surface shows antero-posterior grooves or furrows produced by pressure of projecting hypertrophied muscular bundles of the diaphragm where it overlies the liver. These have been termed diaphragmatic grooves. Orth has, however, seen similar furrows in a seven-months fœtus, and thinks that in some cases, at least, they have a different origin." "Diaphragmatic furrows," such as that in the present case, appear to be connected with compression of the liver at the waist, the position of the furrows (which may be more than one in number) being doubtless determined by ribs or by projecting ridges or folds of the diaphragm. The compression of the liver is evidenced in the present case by a transverse band of constriction and thickened capsule, corresponding to that produced at the waist by "tight lacing." This transverse band of constriction, whenever it is

present, makes the congenital theory of the origin of "diaphragmatic furrows" improbable. "Diaphragmatic furrows" are, moreover, almost certainly connected in some way with pulmonary emphysema and other causes of dyspnœa, probably because dyspnœa leads to pulling inwards of the lower ribs. It is possible, also, that the belt generally worn by labourers may likewise help to produce constriction in some of the cases. I alluded to this point in regard to a similar specimen which I showed at the Society in 1897 ('Trans. Path. Soc.,' 1897, vol. xlviii, p. 113).

The liver in the present case, moreover, showed the peculiar whitish branching lines under the capsule, which are not rarely seen at one or more parts of the organ, especially at the lower and left border of the under surface of the left lobe. These were found to mark the course of thick-walled vessels beneath the capsule. The explanation of the condition seems to be uncertain, and I have not seen the subject anywhere alluded to. From examination of another case it appears that these lines may be due to fibrous tissue surrounding subcapsular blood-vessels, rather than to any special thickening of the vessels themselves. *May 29th*, 1900.

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31. *Heart with complete obliteration of the commencement of the right coronary artery.*

By F. Parkes Weber.

The patient, G. A—, was a horsekeeper aged 40, who suffered from dyspnœa with paroxysmal exacerbations, and died suddenly a few days after admission at the German Hospital (February 1900). He gave a history of having had syphilis at the age of eighteen, but had never had rheumatism. According to his wife's account he began, about February, 1899, to complain of pain in his stomach (apparently epigastric region), and it seemed to him as if something rose to his throat when he lay down. He felt very weak, but about the end of October, 1899, he was so far better that he resumed his work. He gave up work, how-

ever, at the end of December, 1899, complaining of shortness of breath and abdominal pain.

When I saw the patient (February 7th, 1900) he was cyanosed and dyspnœic. The heart was enlarged, and there was a decided presystolic murmur as in cases of mitral stenosis, but there was likewise an aortic diastolic murmur. There was some dulness at the base of the right lung, and the liver was enlarged and hard. The urine was of specific gravity 1020, and contained albumen. Diuretin was employed.

On the 8th February the breathing was fairly easy (28 in the minute). Pulse 73. The urine contained a cloud of albumen.

On the 10th February patient, during a dyspnœic condition, suddenly became collapsed and died.

The heart (weight 24 oz.) was found at the necropsy to be hypertrophied and dilated, and to contain much dark blood. The hypertrophy and dilatation affected chiefly the left ventricle. The aortic valves were somewhat shrunken from sclerotic changes, and water flowed out between them when poured into the aorta. There was no mitral stenosis; the mitral valve was apparently quite natural, as were likewise the valves on the right side of the heart. There was considerable sclerotic change at the root of the aorta; the mouth of the left coronary artery was much narrowed, and that of the right coronary artery could not be found at all. The obstruction of these arteries was, however, confined to their commencements, the channels of both vessels being free outside the aorta.

There was moderate serous effusion in the right pleural cavity, with some adhesion and thickening from old pleurisy. The liver weighed 76 oz., and microscopically showed the results of chronic passive congestion with slight cirrhotic changes. The kidneys were hard and "cardiac"; the capsules could be stripped readily. No undoubted syphilitic changes were found in any of these organs or in the spleen or testes.

Remarks.—There are several points of interest in the case. In the first place, the condition of the coronary arteries is one not rarely found in cases of sudden death from cardiac disease. Thus, in the classical case of Dr. Thomas Arnold, headmaster of Rugby School, who died suddenly at the age of forty-seven, only one coronary artery could be found, and that of small size; as Dr. W. H. Dickinson has pointed out, the other coronary

artery was doubtless there, but escaped notice at the necropsy, owing to its mouth being obliterated as in the present case (see W. Osler, 'New York Med. Journ.,' 22nd August, 1896, p. 250). The same condition was present in a syphilitic woman aged 61, whose case I have already recorded ('Transactions of the Pathological Society,' vol. xlvii, p. 16). The right coronary artery was obliterated at its commencement, and the apparent absence of symptoms in her case was probably due to the other coronary artery being as yet unaffected; she died from a lesion in another part of the body. In both my cases the obstruction of the coronary artery was confined to its root, the portion beyond the aorta being free, showing conclusively that there must have been a complete anastomosis between the two coronary arteries.

Dr. Samuel West ('Trans. Path. Soc.,' vol. xxxiv, p. 67), in regard to Hyrtl's statement that the coronary arteries do not anastomose, suggests that Hyrtl may have endeavoured to inject the hearts immediately after removal from the body, when the presence of clots might cause failure. In Dr. West's experiments the hearts were macerated for two or three days in water, and before injection they were placed in warm water. This was to soften and dissolve any clots present, and he thus succeeded in injecting a series of hearts with gelatine and carmine, sometimes from one coronary artery, sometimes from the other. "Recent observations," says Dr. West ('Trans. Path. Soc.,' vol. xxxv, p. 112), "which have been made independently by Dr. Wickham Legg and by myself, prove beyond doubt that there is not only anastomosis, but a very free anastomosis between the coronary arteries of the two sides; so much so, that the best injection only could be obtained when the mouth of the other coronary artery was closed by ligature or plug. If this be not done the fluid escapes freely from the opposite artery, and can be made even to issue in jets by intermittent pressure." Dr. West has collected a whole series of cases in which one coronary artery was found completely obliterated after death; in this respect some of them are analogous to the present one. In one instance he refers to, both coronary arteries were calcified and obliterated by a cretaceous clot, and the patient (a man aged 56) died from carcinoma without any special cardiac symptoms.

A clinical feature of interest in the present case is that the man suffered from accesses of dyspnœa or "cardiac asthma"

rather than from any form of angina pectoris. This cardiac dyspnœa was likewise a prominent symptom in the case of a man (H. A—, aged 60) after whose death, in March, 1900, I found considerable stenosis in the course (not at the orifices) of both coronary arteries. He had seemed to be somewhat relieved by nitrites.

Another circumstance in the present case also deserves notice, namely, that although a typical presystolic murmur was heard during life, no mitral stenosis was found after death. There was, however, aortic reflux, and Dr. A. G. Phear ('Lancet,' 21st September, 1895), who tabulated forty-six cases of presystolic apical murmur without mitral stenosis, pointed out that in seventeen of them there was aortic regurgitation. The explanation favoured by Dr. Phear, namely, that owing to hypertrophy and dilatation of the left ventricle there is a relative, though not actual, stenosis of the mitral orifice to account for the presystolic murmur, would probably suit in the present case.

May 29th, 1900.

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32. *Pedunculated spindle-celled sarcoma of œsophagus.*

By H. D. Rolleston.

The patient was a man aged 49 years, who died under my care in St. George's Hospital with signs of œsophageal obstruction.

At the autopsy the œsophagus was found to be much enlarged, and before opening was fusiform in shape. The enlargement was due to the presence of a mushroom-like growth arising from its posterior wall in the middle third.

The base of attachment measured three inches in the long axis of the tube. The growth was moulded to fit the lumen of the œsophagus, which it had very considerably expanded. The tumour was pedunculated, especially in the long axis of the canal, and extended from a point one inch from the cardiac end of the gullet to within one and a half inches of the cricoid cartilage.

The growth was white in colour, somewhat friable, and in

places ulcerated. It arose from the submucous coat and carried the mucous membrane in front of it.

There was no infiltration of the tissues around the œsophagus.

The only secondary growths were in the lumbar glands.

Microscopically the growth was a small spindle-celled sarcoma with some areas of necrosis.

Remarks.—Sarcoma of the œsophagus is very rare; examples have been recorded in the Society's 'Transactions' by Targett (vol. xl, p. 76), Shaw (vol. xliii, p. 90), myself (xliv, p. 65), C. Ogle (xlvii, p. 40), and James (vol. xlix, p. 91). Cases have also been recorded by Chapman and by Livingood ('Johns Hopkins Hospital Bulletin,' July, 1898, p. 159). The cases recorded by Targett, Ogle, and Livingood were, like the present specimen, pedunculated, in this resembling sarcomatous tumours of the naso-pharynx.

Most of the cases are histologically spindle-celled, and start from the submucous coat of the œsophagus. The symptoms, preference for the male sex and advanced middle age, are the same in sarcoma as in carcinoma of the œsophagus.

May 29th, 1900.

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33. *Fibrosis of lung following broncho-pneumonia, with remarks upon ninety-five autopsies from the Guy's Hospital records, from* 1875 *to* 1898 *inclusive.*

By JOHN FAWCETT.

J. H— was admitted in October, 1899, under the care of Dr. Hale White. He had been four times previously an in-patient in Guy's Hospital. The only facts of importance in his previous history were that he had had whooping-cough and measles six years before.

He was admitted for the first time in September, 1898, with signs of general bronchitis, and with dulness and bronchial breathing at the base of the left lung. On discharge there were still some râles to be heard at the left base.

He was again admitted in March, August, and September,

1899, each time with an acute attack of broncho-pneumonia, which had supervened upon a chronic bronchitis, the signs of the latter having persisted in the intervals between the acute attacks. With each acute attack there was a rise of temperature to from 101° to 103·4°, and falling with the subsidence of the attack to or about normal.

Autopsy.—Both lungs were very tough, and of a reddish-grey colour. The change was more marked in the left lung than in the right, and especially so in the region of the lung roots. Here some fibrous septa were to be seen radiating out into the pulmonary parenchyma.

The toughness of the lungs was chiefly due to a general increase of fibrous tissue. There was little dilatation of the tubes. The pleura was somewhat thickened over both lungs. Patches of recent broncho-pneumonia were scattered everywhere.

Microscopical examination showed many new vessels in the thickened pleura. Some of the fibrous septa in the lung were continuous with the latter.

There was a general increase of fibrous tissue throughout the lungs, but it was chiefly marked around the vessels and bronchi, and in these spots many new vessels had developed.

In parts the alveoli were encroached upon or obliterated by the chronic hyperplasia, which had affected their walls also. Where the change was in its earlier stages it was seen that the peri-vascular and peri-bronchial tissues were the parts attacked. The alveoli also contained the products of the recent acute catarrhal inflammation. There were no tubercle bacilli present in sections, nor any evidence of tubercular disease. Thus the result produced was a fibroid lining, apparently commencing around the vessels and bronchi, and later attacking the alveolar walls. This was associated with a thickened pleura, from which fibrous tracts extended into the lung substance.

With regard to the ætiology of the disease, it is interesting to refer to the records of ninety-five cases upon which autopsies have been made in Guy's Hospital between the years 1875 to 1898.

In forty-four of the ninety-five cases the chief associated condition is a marked pleural change, and in only five of these forty-four cases is there any history of a preceding acute pulmonary lesion which might have been a pneumonia.

Pleurisy appears, therefore, from this series, to be a more commonly associated condition than any other, and I think it is probably one of the most important ætiological factors in people over twenty years of age.

As to broncho-pneumonia, the commonest cause in children and young people, there were only ten cases in the Guy's series due to this. But only ten out of the ninety-five cases were of ten years or under, and the fibrosis in five of these was thought due to a preceding broncho-pneumonia.

In eighteen cases syphilis was considered to be the cause; in six, chronic bronchitis and emphysema; in three, acute pneumonia, whilst in the remaining thirteen the cause was doubtful.

As to the age at which fibrosis of the lung is most common a considerable difference of opinion exists. Clark and Chaplin consider it to be most common before thirty, and rare after that age. Bastian thinks it most common between fifteen and forty-five years.

In the Guy's series 60 per cent. of the cases were between thirty and sixty.

Thus between	30—40 years . . .	20 cases.
	40—50 „ . . .	22 „
	50—60 „ . . .	15 „

These facts show that if a greater number of cases be taken, including those at all ages, fibrosis of the lung is a disease disseminated over a larger extent of the human life period than has been previously thought to be the case. *May 29th*, 1900.

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34. *Compound dislocation of elbow-joint; complete displacement of humerus forwards; separation of the lower epiphysis of the radius with fracture of the styloid process of the ulna.*

By JOHN POLAND.

THIS specimen was recently placed at my disposal by Mr. Thomas Moore, of Blackheath.

A. E. K—, aged 14, a dock labourer, was admitted into the

Middlesex Hospital on December 26th, 1896, having fallen out of a "swing boat" about twelve feet high to the ground on to his right hand and leg. The radius and ulna were dislocated backwards, whilst the lower end of the humerus projected forwards for two and a half inches through a rent in the skin at the flexure of the elbow. With the exception of the median nerve, which was tightly stretched over the trochlear surface of the humerus, all the soft structures, including the brachial artery, and veins and ligaments of the elbow-joint, were seen to be completely ruptured, leaving the whole of the exposed lower end of the humerus quite bare. The median nerve, like the humerus and all the soft structures, was severely grimed with dust. A simple separation of the lower epiphysis of the radius with deformity somewhat similar to that of Colles' fracture also existed. Primary amputation through the middle of the arm was performed by Mr. Moore, and recovery took place.

On dissection.—There was an oblique rent in the skin two and three quarter inches in length, just below the flexure of the elbow, extending downwards and inwards. Through this wound the whole of the lower end of the humerus and part of the shaft, entirely denuded of soft structures, protruded; over its trochlear surface the median nerve still remained tightly stretched, and grimed with black dirt. The biceps tendon was intact and situated on the outer side of the displaced humerus, while brachial artery, veins, and superficial structures were lacerated. The brachialis anticus and front part of the pronator teres were likewise torn across. The ulnar nerve was uninjured on the inner side of the olecranon. The coronoid process of the ulna was not fractured.

Three X-ray pictures recently (after the amputated arm had been more than three years in spirit) taken by Mr. Moore, and exhibited herewith, show well the great displacement of the articular ends of the bones, and also the appearance of the epiphysis of the internal epicondyle and olecranon as they appear at fourteen years of age. Although these rare cases of compound dislocation of the elbow in healthy children may with very careful cleansing of the wound and reduction of the dislocation be followed by a successful result, yet in this instance the intensely dirty condition of the wound and median nerve, the laceration of the brachial artery and muscles, and the inevitable septic conse-

quences, combined with separation of the lower epiphysis of the radius, rendered any other course of treatment than amputation impossible.

As no attempt had been made to reduce the displaced epiphysis of the lower end of the radius, the characteristic though not severe "back of fork" deformity still existed. The skin over the front and lower part of the forearm above the wrist was much discoloured from extravasated blood. On removing the skin the flexor tendons were seen to be pushed forwards by the projecting end of the radial diaphysis. The angular margin of the diaphysial end was found to have lacerated the periosteum and pronator quadratus, so that to the outer side it projected forwards directly beneath the radial artery, which, however, was uninjured. The lower epiphysis of the radius was displaced backwards one third the way off the diaphysis. The tense condition of the supinator longus attached to the base of the styloid process was as marked a feature as in another specimen I dissected in 1883, the halves of which are in the Museum of the Royal College of Surgeons and Guy's Hospital. I have elsewhere pointed out that this condition of the muscle is doubtless a prominent factor in retaining the epiphysis in its displaced position. The epiphysis itself was not fractured, but four small scale-like fragments of the compact tissue (the largest being three-quarters inch long and half inch broad, and the other half inch long) were detached from the posterior aspect of the diaphysis. The epiphysial cartilage remained with the epiphysis. The periosteum was stripped upwards for one and a half inches from the posterior aspect of the diaphysis, and much blood-clot had been extravasated between these two structures.

The styloid process of the ulna was broken off and displaced to the outer side of the extensor carpi ulnaris tendon. The lower epiphysis of this bone was prominent, and the dorsal branch of the ulna nerve was stretched over it. Its lower epiphysial cartilage in the skiagraphs appears as though partially separated, but this was proved on dissection not to be the case, and my skiagraphic atlas of the normal hand and wrist shows the same. The interarticular postero-cartilage of the wrist-joint was uninjured, though the X-ray pictures show an increase of space between the lower ends of the radius and ulna.

May 1st, 1900.

The four following specimens were also exhibited.

35. *Chronic mastitis in a male sixty years of age.*

By C. D. GREEN.

A swelling had been noticed in the situation of the right breast for six months before the part was removed by operation. There was no history of injury. *May 1st*, 1900.

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36. *Fibroid thickening near the head of the first right metacarpal bone (dorsal aspect) due to the impaction of a fragment of glass for eighteen months; removal by operation.*

By JOHN VALÉRIE.

February 20th, 1900.

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37. *Cerebro-spinal meningitis (bacteriology undetermined)*

By A. J. CLEVELAND and JOHN FAWCETT.

May 29th, 1900.

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38. *Colloid carcinoma of the breast.*

Changes arising in the cells; the stroma unaffected.

By CORRIE KEEP.

May 1st, 1900.

39. *Two cases of myxœdema.*

By Cecil F. Beadles.

Two years ago I demonstrated by means of lantern slides at this Society the minute changes that were to be found in three cases of myxœdema, and a full account of these is published in the 'Transactions' for 1898. I am now able to add two further cases to the series which by chance have fallen to my lot to examine. They are both females who died insane in Colney Hatch Asylum, and both had well-marked myxœdema. The first had long been subject to epileptic fits, and her death was the immediate result of a prolonged succession of epileptiform seizures. Her thyroidal disease was far advanced, but she had undergone the thyroid treatment for a period some years before, and recommenced it after her admission.

The second case was not recognised as suffering from myxœdema until a year after her admission to the asylum, though its onset probably anteceded that date. She underwent the thyroid treatment for a time. There was the association of an epitheliomatous growth on the nose, a fact interesting when it is remembered that the third case recorded had what may be termed an early adeno-carcinoma of the stomach. Erysipelas commencing from the edge of this growth spread over the face, and the patient apparently died from the spread of inflammation to the mucous membranes and the absorption of the poison into the system.

In both cases the heart was in an exceedingly fatty state, the muscle of the myocardium being largely replaced by fat cells, and in both all the smaller arteries of the body presented thickening of their walls from hypertrophy, mostly of the muscular and subendothelial coats, with more or less hyaline degeneration of these tissues. The connective tissue throughout the body was of the pale granular kind peculiar to myxœdema. In neither was there excessive vacuolation of the fat-cell nuclei.

In the second of these cases only did the lungs present special features of interest, where, in addition to the usual chronic changes in the arteries, thrombosis of some of the smaller vessels

was found, evidently the result of the acute specific disease; and the presence of dense fibrous and fibro-hyaline deposits of cartilage-like character similar to those found in two of the former cases of myxœdema, and which would seem to be dependent on the myxœdematous process.

The thyroid gland in both was greatly atrophied; there were scattered nodules embedded in the connective tissue, which proved microscopically to consist of an intermingled mass of degenerated epithelial cells and of small, round, inflammatory corpuscles. There is scarcely any trace of true thyroid vesicles to be found in either case.

The pituitary body in both was slightly above the average in size and weight. The weights were thirteen and eleven grains respectively, and their measurements in parts of an inch were—

Case 4: transverse, $\frac{11}{16}$; antero-posterior, $\frac{7}{16}$; vertical, $\frac{4}{16}$.

Case 5: „ $\frac{10}{16}$; „ $\frac{7}{16}$; „ $\frac{4}{16}$.

The increase is due to enlargement of the glandular portion of the pituitary, in which the microscope shows the presence of an excessive colloid formation throughout that lobe, with irregularity and enlargement of the epithelium.

Of the five fatal cases of myxœdema, none of the last four has shown anything like the increase in size of the pituitary that was present in the first. This is probably due to the fact that none of the four subsequent cases were in so advanced a stage of the disease, the degenerative processes having been held in abeyance by the treatment they underwent with thyroid extract, the first having died before this method was introduced. The same may account for certain more advanced degenerative changes in the tissues of Case 1, viz. the excessive vacuolation of fat-cell nuclei, endarteritis obliterans, and particularly the changes in the vessels of the lung, and the greater frequency of the cartilage-like deposits in the alveolar spaces of that organ.

Following is a detailed account of the two additional cases which are referred to as Case 4 and Case 5.

Case 4. *History.*—L. P— (female, 13,604) was admitted into Colney Hatch Asylum on March 8th, 1898, with the dementia of myxœdema. She was fifty-seven years of age, and had the characteristic facial appearance of myxœdema in a fairly advanced stage. Abnormally stout, weighs 8 st. 12 lbs.; height

5 ft. 6 in.; œdema of the body, which did not pit on pressure, noticeable in the face, hands, and feet. Hands spade-like, fingers broad and thick. Skin thick, coarse, and rough; scaly, especially about the ankles and feet. Face œdematous, with features broadened, eyelids swollen, lips thick, neck full and puffy, tongue large. Hair of a dark brown colour, scanty on the head, and almost absent from the eyebrows and eyelashes. Some downy hairs on the face.

All the special senses were blunted; both hearing and eyesight were impaired, the left pupil was a little larger than the right. Voice slow and husky. Temperature subnormal. Pulse 64, slow, but fairly regular; mitral cardiac murmur, and aortic sounds altered in character. Breath-sounds weak and bronchial in both sides of the chest. Urine acid, thick with epithelial deposits; did not clear upon boiling, but turned a brownish tint when boiled with liquor potassæ; it did not appear to contain any albumen. She passed thirty-six ounces in the twenty-four hours, two days after admission. She complained of numbness of the fingers, and felt the cold severely.

Her mental condition was that of dementia. She was dull, and her general intelligence much impaired; her memory very defective. The certificate stated that "she seems quite lost in her mind, and totally unfit to look after herself; she is violent and assaults the attendants." She had been a month in the workhouse.

A daughter stated that the patient had been a widow twenty-four years; she had two children, who were thirty-five and thirty-seven years of age; there was one miscarriage. Her condition was thought to be due to change of life, which occurred eleven years ago. Six or seven years ago her face and hands began to swell; it commenced in the hands first, in the form of rheumatism, where she complained of intense rheumatic-like pains. Her fingers became so stiff, as the result of having to hold her hands in a special way at her work as an artificial flower-maker, that she was obliged to hold them over a mug of hot water to keep at her employment. She had a hard life to earn a living, and was very abstemious. Two years ago she had a fall and fractured her right arm. She had not been able to bend the left arm properly owing to an injury when a baby. Ever since a girl of about seventeen she had been subject to fits, but they

[illegible] which she had [illegible] and
[illegible] in the
[illegible] Christmas
[illegible] and
[illegible] having
[illegible] as an
[illegible] and was treated by
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[illegible] appearance is
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[illegible] and she was less
[illegible]

[illegible] she was put on
[illegible] of powerful extract
[illegible] March 20th.
[illegible] the thyroid,
[illegible] She appears to have
[illegible] under the treatment at the
[illegible] that she
[illegible]

[illegible] the taking of a
[illegible] The face was thinner, the œdema and
[illegible] her body-weight had
[illegible] The pulse only [illegible] showed a subnormal
[illegible] about the right, but with an occasional slight
[illegible] the administration of the drug, though of late the
[illegible] and only slightly subnormal. The
[illegible] owing to the patient taking
[illegible] only after she began to refuse altogether.
She continued to lose weight. On June 1st she was kept in bed,
she refused everything, would not speak or do anything she was
asked, but appeared to understand perfectly. She was heavy
and drowsy, but did not sleep at night. She lay with her eyes
closed and forcibly prevented their being opened, turning her
eyeballs downwards. Pulse was feeble. She was given beef tea
by the œsophageal tube. During the next few weeks she
recovered strength and got up, but was disinclined to exert her-
self; her weight had risen again to 7 st. 10 lbs. on July 10th.
On July 30th she went to bed feeling generally weak.

At 11.45 a.m. on August 2nd she had a severe epileptiform

seizure; both legs were drawn up, the whole body convulsed, and she was totally unconscious. She came to and had a similar seizure at 3.45 and again at 7.45 on the same day. At 1 p.m. on August 3rd a succession of convulsive attacks began, which continued up to 4 a.m. on Augnst 4th. Eighteen independent attacks were counted during the first three hours. These were all identical in nature, and were of a peculiar character. The head, which during the interval had been lying turned a little to the right side with the eyeballs directed to the right, slowly began to move towards the left; a slight twitching commenced on the face beneath the right eye and spread down the face to the angle of the mouth on that side; then, more suddenly, the whole face on both sides went into spasmodic contractions. The head, drawn to the left side, was violently jerked, and the eyeballs, though moving from side to side, were strongly deviated to the left. She foamed at the mouth and became purple in the face. Before these movements had reached their maximum intensity the left arm, which was lying flexed across the chest, began to be drawn up, the fingers, wrist, and elbow in order became flexed, and the arm slowly twisted outwards and a general convulsive movement of the limb took place, followed by rigidity and similar movements of the left lower limb, which was the while extended outwards and separated from the right limb. The right side remained limp and not convulsed. The whole seizure lasted little more than two or three seconds; it ceased more or less suddenly. The arm went back across the chest, the head slowly moved again to the right side, with the pupils directed strongly to the right. Both pupils throughout remained equal. Her temperature was 100°. During the interval, which was a trifle longer than the convulsive stage, the patient seemed to be semi-conscious; there was no indication of feeling the prick of a pin; conjunctiva reflex was present. At 6 a.m. on August 4th she was moving her head from side to side, but there was no movement of the limbs. At 7.45 the fits recommenced, and now affected both sides of the body, seeming now to commence sometimes on the right side and sometimes on the left. Similar seizures continued all day at short intervals up to the time she died, which took place at 5.20 p.m. She was unconscious since 1 o'clock on August 3rd, but there was entire absence of prolonged coma. Breathing gradually became more shallow,

It was thought possible that a cerebral hæmorrhage had occurred.

Autopsy.—The body was well nourished but not excessively fat. The characteristic aspect of myxœdema had considerably lessened, but was still noticeable in the thickening of the skin about the eyelids, nose, and lips. The skin of body was of natural aspect, not thick or scaly. No œdema of legs. Hair on head and pubes plentiful, almost absent in the axillæ; some downy hairs on the face and upper lip. Tongue pale and only slightly enlarged.

Superficial fat not excessive, and comparatively little beneath the peritoneum. This tissue everywhere had a fairly healthy appearance. The voluntary muscles were of a normal tint. A small hæmorrhage had occurred in the left sterno-thyroid. Bones a trifle brittle. No tumour or new growth found in the body. Slight congestion of the lining of the trachea.

Heart slightly dilated and also hypertrophied. There was excess of natural fat on its surface; a considerable thickness of the ventricular walls was pale and soft from fatty infiltration. Valves fairly healthy. A slight degree of atheroma of the first part of aortic arch. Pericardial cavity filled with serous fluid.

Lungs not adherent, and not distended; they were dark and congested, and contained some frothy fluid, but there was no recognisable pneumonic consolidation. A few hard, pigmented, pea-like nodules were scattered superficially about both organs, and there was a small mass of caseous matter at the right apex, indicating a previous state of early tubercle.

Stomach dilated and contained much mucus. A few petechial hæmorrhages scattered about the mucous membrane. The pylorus hard and slightly contracted. Intestines healthy.

Liver small and deeply congested. Gall-bladder filled with dark fluid bile and contained one calculus, size of a large cherry, weighing 43 grains, and composed mostly of cholesterin.

Pancreas softer than natural. *Spleen* small, firm, and dark.

Kidneys of about equal size, length 3½ to 4 inches. Both very congested. They were hardened, but their capsules were free. Bladder normal.

Uterus contained a large calcified fibroid on the right side, size of an orange, and a non-calcified one of rather smaller size on the left side; also a small subperitoneal fibroid in its anterior

wall. Its cavity and os somewhat more patent than usual. Both *ovaries* small and healthy.

Head.—The calvaria as removed weighed 11½ oz., the bone of moderate thickness. Some excess of fluid present. The finer membranes were a trifle thickened in places, not adherent, and were congested over both hemispheres; there was no large hæmorrhage, but there were a number of small blood extravasations beneath the pia arachnoid on both sides. The basal arteries healthy.

The *brain* was of somewhat small size, exceedingly softened and congested throughout; the cut ends of small vessels stood out prominently. Small petechial hæmorrhages were scattered about throughout the grey matter at the base and the adjoining white substance. The lenticular nucleus in places presented a more yellowish tint than normal, especially that on the right side. Ventricles slightly dilated, ependyma congested, more particularly that in the right posterior horn. At the outer border of the right cerebellar lobe was marked softening. The grey matter in places was distinctly discoloured, being of a more yellowish tint than natural. The grey matter around the iter was of a gelatinous character apparently from œdema of the neuroglia. The substantia nigra of the mesencephalon seemed unusually marked on the right side.

The *pituitary body* was rather larger than the average gland, clearly due to the lateral lobes of the glandular portion, the posterior lobe being if anything reduced in size. Its appearance and colour were normal. It weighed 13 grains (·9 gramme).

Thyroid gland greatly atrophied and of pale tint. It was represented only by two small lobes with no central connecting portion. No very distinct nodules could be felt, but a slight degree of thickening could be made out in places.

The weights of the organs were—

Brain	36 oz.
Heart	10½ „
Lung, right	19 „
„ left	18½ „
Liver	28½ „
Kidney, right	4 „
„ left	4 „
Spleen	2¼ „

Histology of the tissues and organs.

The hardening agents employed were a 3 per cent. solution of formalin and Müller's solution; the sections were cut by the freezing method and stained with logwood.

Skin from the chest exhibits only slight change. The rete mucosum of the epidermis is deeply stained and clearly differentiated from the pale swollen cells of the horny layer, which is increased in thickness. The appendages are natural with the exception of hairs, which are degenerated. The cutis vera is composed of loosely arranged fibro-hyaline tissue but little nucleated; many of the fat cells in the deeper parts have vacuolated nuclei. Small blood-vessels show thickening of their walls; the smaller vessels stand out conspicuously, and have an increase of deeply staining round-cells immediately around them.

Subcutaneous connective tissue is composed of loose bands and single fibrils of fibrous tissue with a sparcity of nuclei. The cells composing fat lobules are somewhat small, and many have a vacuole in their nucleus.

Small arteries throughout the body have some thickening of their walls, mainly an increase of the middle coat, but some with a distinct proliferation of the inner layer, causing a narrowing of their lumen. Muscle tissue stains deeply.

Muscles, judged by the pectoralis major, have their fibres held together by a fibro-granular material of pale colour in which are contained the small vessels and nerves; their cross striation is feebly marked. The left sterno-thyroid muscle is in the same condition, and here there is a deposit of some size mainly composed of a fibrinous network with a round-celled infiltration at its edges, which is evidently the remains of an old blood extravasation.

Small nerves in the subcutaneous tissue and amongst voluntary muscle-fibres are pale and swollen; in the former site the nerve bundles are more distinctly separated from their outer sheath. The larger nerve-trunks, as seen in the vagus, are in a similar condition, the perineurium around the funiculi being separated from the fibres, and the epineurium having a loose texture.

Heart.—A section through the wall of the left ventricle

reveals an excessive fatty infiltration of the myocardium, the former dividing the muscle tissue for the most part into very small areas. Individual muscle-fibre cells are loosely connected together; their striation is indistinct, and in some places they are granular and contain brown pigmentary particles. The intervening connective tissue is of a delicate fibrinous character containing elongated nuclei, and in the larger septa, where groups of fat cells exist, these cells are of small size, and a few show vacuolation of their nuclei. The peri- and endocardium is of the same loose character; in neither were any collections of round-cells seen; the fat cells, however, pass close to the outer covering of the organ. The smaller branches of the coronary arteries have distinct proliferation of their inner coat with consequent restriction of their lumen.

Lungs.—Various parts of both organs were examined without discovering any of the minute cartilage-like masses that were found in two of the previously recorded cases of myxœdema. Sections of lung tissue show a general engorgement of the vessels and capillaries of the alveoli. The walls of some are homogeneous in structure, from changes of a hyaline nature in the muscle tissue. In some parts of the lung the air-spaces are filled with a fibrous exudation. Cellular deposits occur in places, composed both of red blood-discs and small, round, logwood staining cells; but these pneumonic patches are almost microscopic in size. Several of the fibrous nodules were examined, but none presented signs of active tubercle. They are made up of a group of small circular areas composed of dense fibro-hyaline tissue, in the centre of some of which is an amorphous caseous-like material, free from nuclei, that has partly undergone calcification. The outer part of the nodule is formed of loose fibrous tissue containing a black pigmentary deposit, the latter extending beyond into the neighbouring alveolar septa. No giant-cells are seen. The pleura is thickened, especially where the nodules exist, and contains small collections of inflammatory cells embedded in a hyaline stroma, pierced by vessels with thick muscular walls.

Liver.—In various parts the hepatic cells stain indifferently and have slight pigmentation, but an absence of fatty infiltration. The connective tissue of Glisson's capsule has a loose granular structure, and there is an increase of nuclei in places, but a more

marked feature is the presence of a black pigment in this connective tissue. Here and there are distended spaces filled with a colloid-like substance.

Spleen.—In this organ the arteries show undoubted hypertrophy of their walls, the lumen of some being almost obliterated. There is much pigmentary deposit scattered about the splenic pulp and unnaturally abundant outside some of the vessels in the thickened trabeculæ. No change in the lymphoid cells is recognisable.

Pancreas.—The glandular tissue is greatly atrophied. The stroma, increased in amount, is formed of structureless fibrous tissue with scattered groups of inflammatory cells. Smaller branches of the pancreatic artery have thick walls. Transverse section of an artery the size of a hemp-seed shows a marked condition of endarteritis, the calibre of the lumen being diminished by growth from the inner coat, that has a pale granular structure.

Submaxillary gland.—A section made from the right gland shows an inflammatory condition. There are many small collections of leucocytes situated in the perilobular septa in the vicinity of the ducts and vessels. Glandular epithelium seems healthy.

Stomach.—The pigmentation is the result of blood extravasation into the superficial part of the mucous membrane, and there is a round-celled infiltration at some parts of the surface. The connective tissue of the submucous coat is hyaline in nature, and the nuclei of some of the fat-cells are vacuolated.

Kidneys.—The epithelial cells of the cortical tubules are mostly granular, and their nuclei faintly staining. A few of the glomeruli are degenerated into hyaline spherules. The stroma is composed of pale, loosely formed connective tissue, increased in amount. No inflammatory cell collections are seen. Some of the larger blood-vessels have localised thickening of their walls, and there is increase of connective tissue around.

Brain.—Perivascular spaces of smallest blood-vessels and capillaries are much distended, and in some there is blood pigment. Round nuclei are unnaturally numerous on these vessels.

Pituitary body.—A median antero-posterior vertical section does not reveal a cyst of any size, but about the centre of the

boundary zone is a group of colloid-containing vesicles of comparatively small size and about a score in number. These cysts are mostly lined by a single layer of compressed epithelium, and the remains of epithelial cells are embedded in the colloid matter within. Throughout the anterior lobe the epithelial cell masses are of about normal size; the cells for the most part are small, but some large cells are scattered about which are swollen and contain colourless globules or vacuoles. Scattered throughout the epithelial masses are spherules of colloid, most abundant towards the anterior part of the lobe; these stain more deeply than does the colloid within the cysts at the boundary zone,—a feature that is noticeable in the pituitary of all the cases of myxœdema. At the lower and hinder part of this lobe is a group of cells in which the cell masses are larger, and the individual cells are more deeply staining, as though undergoing active proliferation. There is a loose intervening connective tissue with distended capillaries and lymphatics, both of which are filled with a feebly staining amorphous deposit very different from the dark colloid spherules amid the epithelium. Larger blood-vessels are scanty. The posterior lobe is formed of loosely arranged fibrous tissue with some colourless amorphous ground material. It is free from pigmentation.

Thyroid gland.—A portion of the gland was taken from the lower and outer part of the left lobe. This was firmer to the feel than the remainder of the lobe, and on section there could be seen with the naked eye four or five small oval masses of a fawn colour, having the diameter of about one eighth inch, and lying embedded in a loose white fibrous tissue. Sections were prepared after hardening in a 4 per cent. solution of formalin. A section measuring five eighths inch by four eighths inch contains four of these larger localised oval areas; they stain deeply, and are sharply marked from the connective tissue in which they lie. These are the so-called lymphoid nodules found in the thyroid of myxœdema. Besides, the section contains a number of smaller areas less defined in outline and taking a colour midway between the two former structures.

Under a low power of the microscope the stroma, which composes the greater bulk of what remains of the thyroid gland, is found to be composed of dense fibro-hyaline tissue, in which are thick-walled vessels and vascular clefts with little or no true wall,

and which are presumably of a lymphatic nature. Scattered about are various-sized collections of small round inflammatory cells, which in places seem to be undergoing replacement by young connective-tissue nuclei. It is the larger of the round-cell masses which give rise to the ill-defined areas, as seen in the stained section with the naked eye. Here and there amongst these cells a few remains of the thyroid epithelium may be seen. Under an inch objective the larger deeply-staining areas look like lymphoid tissue, and only with difficulty is any trace of the original thyroid tissue seen, represented as it is by a few circular openings or small masses of epithelium cells.

Examined with a one sixth inch objective the fibrous stroma presents a dense semi-hyaline structure with elongated connective-tissue nuclei, and foci of deeply staining round-cell infiltration. The appearance is strongly suggestive that the inflammatory cells are gradually replaced by connective-tissue cells, and then by the ground-glass like homogeneous tissue. Amongst the round cells are newly-formed capillary vessels where, as in the denser tissue, the vessels are thick walled, and often hyaline in structure, the lumen of some quite occluded. Most of these round-cell masses contain slight traces of the pre-existing thyroid tissue, either in the form of isolated or minute groups of epithelial cells, small colloid masses, or more rarely minute vesicles surrounded by a layer of atrophied cells. One of the small dark areas consists entirely of atrophied thyroid tissue,—small cell groups of compressed and irregular epithelium; a few of the cell masses have a minute space amongst the epithelium, the remains of the former vesicle. Scattered about the stroma are a few isolated small spaces lined by epithelial cells, either in single row or massed together in places, and some partly filled with these cells. These are alveoli, or ducts cut off by the replacing connective tissue. The large "lymphoid" areas contain further traces of the thyroidal epithelium. Here faintly staining degenerated epithelial cells are irregularly scattered amongst small, round, deeply staining inflammatory cells. There is an entire disappearance of the normal vesicles. The degenerating epithelial elements are compressed amongst those of inflammatory origin. A few small colloid spherules are met with, but very sparsely. There is no arrangement of the epithelium in columns, such as occur in the parathyroid, and there can be little

doubt that these cells are of the thyroid proper, atrophying before an inflammatory process, and slowly becoming replaced by chronic inflammatory tissues.

Case 5. *History.*—M. W— (female, 12,667) was admitted into Colney Hatch Asylum on April 27th, 1896, under the following certificate:—"Has great loss of memory, incoherent in her conversation; has delusions; says she shut herself in her room by command of the Lord, who requested her not to open the door. She says the Lord was talking to her last night about cats and devils. She fancies the devils are putting devils to death. She says also that all things belonging to God also belong to her." She was also said to be dirty in habits, and continually chattering that there is no sense in anything. The cause of her mental condition was unknown, but it was stated to be of two months' duration.

She was a big, heavy-looking woman, weighing 14 st., said to be affected with no physical defect beyond an "ulcerating wart on the left side of the nose." Mentally she was dull, depressed, and apathetic. During the following month she occasionally refused her food and had to be fed with a tube. In June she seemed better both mentally and bodily, but this was not permanent, and delusions of a religious nature returned. On March 6th, 1897, it is first noted that she had signs of myxœdema; her skin was dry and swollen, her speech slow. It is probable, however, judging from a photograph taken on admission, that she was then in an early stage of the disease. A month later the myxœdema was more pronounced, and she was put on thyroid extract powders twice a week, which was associated with no ill effects. The ulcerated wart was now regarded as either an epithelioma or rodent ulcer. Six months later the myxœdema had improved, but the growth had increased in size, and this continued to slowly spread.

The following note was made on September 18th, 1898:—She has been gradually getting more infirm, more stooping, more œdematous, and more impaired in intelligence from the time of her admission up to now. She is very stout, and weighs 14 st. 9 lbs. Her appearance is that of well-marked myxœdema. Face puffy, skin thick and rough, features somewhat blunted; some œdema of the eyelids, lips thick, tongue not appreciably enlarged.

Hair on head grey, thin, and scanty. Eyesight impaired, for which she wears glasses. Hearing defective. Speech thick, slow, and drawling. Hands markedly spade-like, skin thick, fingers broad. Fulness of neck. Legs and feet very swollen, œdematous-looking, but not pitting on pressure; skin thick and rough. She is always up, but is very infirm, and can only walk with the aid of a stick; has great difficulty in raising herself to a standing position, and then her back is greatly bent and her knees flexed. Always feels the cold very much, and has to be wrapped up in flannel during the hottest weather. Temperature in axillæ 97° in morning, 98° in evening. Pulse 58, full and slow. About nine months ago she had a severe bronchial attack, and has been far worse since; her temperature then reached 99°. at other times it has usually been found slightly below normal, She has never had a fit or faint. There is a circular ulcer on the left side of the nose, now the size of a shilling, with raised red edges and central depression; this has been slowly getting bigger, but more so during the last nine months. Has no pain in it, and has persistently refused to have the growth removed. It is typically epitheliomatous in character. She believes herself "cancerated" all over her inside. Her mother died of cancer of the arm, for which she underwent several operations; other relatives on her mother's side also died with cancer. She has one son living, a daughter dead, and she had several stillborn children, for whom instruments were used. Her intelligence is considerably impaired, and she is more or less demented; but she gives fairly rational replies to questions. Her forehead is very narrow, and the whole of the cranial portion of the head is small. The lower jaw seems large and broad. There seems a slight degree of paresis on left side of face, which is not always noticeable.

Her son gives the following history:—Patient has been bad on her legs for years, and not able to walk much. She has been stout as long as he can remember, but he does not know when her face first became puffy. Up to eight years ago she was a cook; she then gave up work, and has since broken down in health. Her mind seems to have been more or less affected for twenty years; there was a tendency to religious mania; she was continually reading religious books, and would sit up at all hours of the night to do so, finally shutting herself up in a room,

saying she was locked in by the hand of God. She had periods of depression: never had a fit or loss of consciousness. Her eyesight had been bad for twenty-five years. Speech slower the last three years. She never had prominence of the eyeballs. Four years ago a pimple appeared on the nose; various ointments were applied without effect, but the top came off. Her mother died of cancer, her father of a paralytic stroke. No insanity in family. Married thirty-three years. A widow some years; children as stated by herself.

From this time she continued to grow more demented and incoherent in speech. The growth on her nose continued to increase, but there was little further change as regards the myxœdema. Towards the end of February, 1899, erysipelas developed, starting from the edge of the growth, and spread over both sides of the face. On March 4th she seemed to have almost recovered from the erysipelas, but was left very weak, and she gradually sank and died on March 8th, at the age of seventy.

Autopsy.—The body was exceedingly obese, probably weighing from 18 to 19 stone. The appearance that of well-marked myxœdema. Skin white and smooth with no scales, and not pitting on pressure. Hair in fair amount on scalp, scanty on eyebrows and eyelashes, and on the pubes and axillæ; there was none about the body. The epitheliomatous growth on the side of the nose had reached the size of a two-shilling piece. No warts or growths elsewhere. No fluid in any of the serous cavities. Tongue not appreciably enlarged.

Fat was in great excess both on the parietes and within the abdominal cavity in the folds of the omentum. It was of a deep orange tint.

Skeletal *muscles* seemed distinctly wasted, and replaced in part by fat. The muscle tissue was of a deeper red colour than natural. The muscles covering the larynx were atrophied and embedded in a mass of dark fat.

The inner lining of the pharynx, larynx, trachea, and œsophagus was intensely congested.

Heart enlarged and dilated, in a very fatty state. A thick layer of adipose tissue covered the outside and replaced much of the myocardium, which was soft and pale, and had streaks and spots of fat scattered amongst the muscle throughout the ven-

tricular wall. Both sides of the organ were filled with blood-clot, that on the right side being colourless. The endocardium was deeply blood-stained, and the intima of the aorta was similarly affected. Mitral orifice dilated and its valve-flaps puckered. Aortic cusps healthy. The aorta and all its larger branches were atheromatous, and there was a marked degree of this condition around the orifices of the coronary arteries.

Lungs both a little adherent. They were dry on section, and the lining of the bronchial tubes was congested throughout. A number of small, hard, fibrous nodules were felt in and on the surface of both organs. No pneumonic consolidation and no sign of tubercle.

Intestines inflated, peritoneal covering in parts was congested.

Stomach natural.

Liver of fair size, very soft, and seemingly fatty.

Kidneys of natural size, congested and fatty. Small localised fatty areas scattered over the surface. Capsules free. The left kidney contained a cyst, size of a cherry, near the surface, but not rupturing on removal of the capsule. Much fat in the pelvis of both organs.

Bladder greatly dilated.

Supra-renal bodies of a very dark tint, the right soft and smaller than natural.

Uterus very atrophied. Os widely opened, and the cavity of the cervix and body dilated and filled with dark mucus, the lining being congested.

Both *ovaries* exceedingly small and atrophied.

Head of peculiar shape, the cranial portion being very much narrower than the lower part of the face. Calvaria somewhat thinned and translucent in many parts; diploë congested. Cranial cavity of small size.

Brain small, but weighing 42 oz.; convolutions well formed, and no local wasting. A little general thickening of the pia-arachnoid membrane with adhesion of the frontal lobes. Arteries at the base in an advanced state of atheroma with dilatations in places. Brain substance firmer than natural. The right lateral ventricle a little larger than the left, and the grey ganglia at the base on the right side more flattened and spread out than on the other. There was no sign of old or recent hæmorrhage.

Pituitary body of about normal size and appearance, but seemingly harder than natural. Posterior lobe well developed, peduncle thick. It weighed 11 grains (·8 gramme). Firm and compact on section.

Thyroid gland very atrophied. It was represented by two small lobes, the left a little the larger, with entire absence of the central portion. A number of hard fibrous-like nodules could be felt scattered about the substance of the gland.

The weights of the organs were—

Brain	42 oz.
Heart	14 „
Lung (right)	14 „
„ (left)	12 „
Liver	50¾ „
Kidney (right)	5 „
„ (left)	5¼ „
Spleen	3¼ „

Histology of the tissues and organs.—The reagents employed were similar to those in the last case.

Skin.—There is nothing very characteristic of the disease to be observed in a section prepared from the integument of the chest. Both the epidermis and connective tissue are fairly normal. No hair follicles are present. Blood-vessels are few and appear healthy, except some thickening of walls.

Subcutaneous connective tissue is composed of fibrous bundles, with but few nuclei. Fat cells are large and have a degenerated appearance; their nuclei are badly stained, and no vacuolation can be made out.

Heart.—Section through the wall of the left ventricle presents a superficial layer of fat one-eighth of an inch in thickness, from which thick bands of fat cells pass deeply into the muscle tissue; they carry the blood-vessels, which have little support beyond that obtainable by immediate contact with fat cells; the nuclei of a small proportion only are vacuolated. In the deeper part of the myocardium there is an excess of delicate, loose, fibrillated connective tissue dividing up the muscle tissue, and which contains the vessels. Some of the smaller intra-muscular septa have an increase of connective-tissue nuclei and minute collections of small round cells. In many parts the individual muscle-fibre

cells are loosely connected together; these are often granular, and show some pigmentary degeneration. The endocardium is composed of a pale, loose connective tissue, and contains collections of inflammatory cells. Small nerves show no appreciable change. The smallest arteries have greatly thickened walls. A larger vein is occupied by a thrombus (*ante-mortem* clot).

Lungs.—There is engorgement of the capillaries and arteries throughout, with some thickening of the small artery walls, that of some of the smallest being in a state of hyaline degeneration. Some sections show fair-sized vessels blocked by a thrombus, which from its structure would seem to be of a septic nature; the central part is composed of pure leucocytes, that beyond by a semi-organised, deeply staining mass, containing white and red corpuscles, and around part of the edge is a fibrinous network entangling only red blood-discs. These vessels appear to belong to the arterial system, and most indicate a distinct subendothelial thickening on one side of their circumference.

Several of the superficial hard nodules, which vary from one eighth of an inch to a quarter of an inch in diameter, were examined microscopically. Dense, fibrous-like tissue encircles a central focus of broken-down cells and *débris*, the whole reaching the size of a miliary tubercle, but exhibiting no active cells and no tubercular giant-cells. These are embedded in a strand of coarse fibrous tissue containing much black pigment and clusters of inflammatory cells. It is not quite evident whether these nodules are the result of previous tubercular infection, for the condition might readily be produced by a thrombosed vessel with subsequent changes in and around its walls.

The pleura is thickened by dense fibrous tissue containing much pigmentary deposit, and from it thick septa extend into the lung tissue. Scattered about the organ are areas in which the alveolar spaces are filled with a fibrinous or red corpuscular exudation. The walls of some of the comparatively small bronchi show an actual inflammatory condition with an infiltration of small round cells; the cartilage of these tubes is normal to look at.

A number of the *cartilage-like* deposits have been found in the lung, such as were described as being present in two of the cases that were previously recorded by myself. These are solid masses, deeply staining with logwood, but so small that few are

visible to the naked eye even in stained sections. The largest appear in unstained sections as pale specks, and would be passed over if their presence were not suspected. Once seen under the microscope their structure is peculiar and characteristic. They are composed of dense, hyaline-like tissue, pierced by a number of small openings, which look much like the lumina of small vessels. There is usually an irregular, wavy, and concentric marking of the hyaline material, due to difference of intensity in the staining, but indicating no histological structure. The edge is sharply marked, and frequently takes the deepest tint. Scattered through it are a number of small nuclei. The mass, taken as a whole, has the appearance of imperfectly formed cartilage, but it has not the structure of the cartilage of the bronchial tubes, or that of any of the established forms of normal cartilage of the human body. The nuclei are not those of cartilage; they resemble more the elongated nuclei of fibrous tissue, being smaller and more lengthened than those of bronchial cartilage, and far less numerous. A wedge-shaped mass of this nature is present in a broad fibrous septum some distance from the pleura, where it lies in close contact with the outer wall of an artery. Another mass, which reaches the size of a pin's head, has an irregular contour, but lies surrounded on all sides by air-spaces, with no septa of any size in the immediate neighbourhood. These masses exactly resemble the larger ones found in the other two cases. They give one the impression that they originate from an exudation in the tissues and air-spaces which has undergone gradual change in its composition, terminating in solidification.

A number of sections taken from different parts of the lung contain these cartilage-like deposits, but they are nothing like so plentiful as in the first case described. No what may be called fully-formed deposit of sufficiently small size to occupy only a single alveolar space was found in the present instance (such as that figured in the 'Pathological Transactions' for 1898), but there are a number of the paler staining fibro-hyaline deposits, which I am inclined to think are an earlier state of the same condition. Sparsely scattered about one comes across single alveolar spaces, or perhaps groups of two or three that are entirely occluded by a solid spherical mass of dense tissue, in which are embedded connective-tissue cells. These deposits

exhibit a more or less fibrous structure, and they do not stain with the same intensity as the larger irregular masses. I venture to think that the cartilage-like masses are the result of a further degenerative change in these smaller deposits, which have become fused together and the intervening alveolar walls obliterated.

Liver.—The portal canals present an acute inflammatory state, being crowded with leucocytes amounting almost to miliary abscesses. The adjoining capillaries contain an excess of white corpuscles, and there are small collections of inflammatory cells scattered in places amongst the liver cells. It is obvious that this condition is the result of a general blood infection, and is doubtless due to absorption of the erysipelas poison from which the patient died, and has no direct relation with the disease due to changes in the thyroid gland. Apart, however, from this acute condition, there is marked increase of connective tissue of Glisson's capsule, and the arteries show excessive thickening of their walls, by which some are almost occluded. The capillary network in parts of the liver is greatly distended, and the intervening hepatic cells are much flattened and atrophied. In some regions the hepatic cells show a slight degree of pigmentary degeneration, many of their nuclei are swollen; there is only a very little fatty infiltration here and there. Colloid-like masses exist in some vessels.

Kidneys.—Both signs of acute and old chronic nephritis exist. The former is responsible for clusters of round inflammatory cells in parts of the stroma, mostly in the neighbourhood of the larger vessels, and also immediately beneath the capsule. Some red discs are extravasated into the stroma from the engorged glomerular network of capillaries. Unnaturally deep staining hyaline casts occupy a large proportion of the longitudinal tubules of the pyramids. The epithelium is granular with indistinct nuclei in places; an advanced condition of this, amounting practically to necrosis, exists at those parts of the surface that appeared as fatty areas to the naked eye. The more chronic changes are responsible for thickening of the arterial walls of the larger vessels in the boundary zone, and a hyaline state of a few of the glomeruli.

Brain.—The vessels of the pia mater and septa passing into the brain have their coats thickened and undergoing hyaline

change, and the vessels contained in the adjoining nerve tissue are surrounded by dilated perivascular spaces filled with round cells or amorphous deposit. These conditions seem especially marked about the base of the brain and in the optic commissure.

Pituitary body.—The fibrous capsule has blood extravasated into it, and contains arteries with thick walls and marked sub-endothelial overgrowth. At the boundary zone only a small group of comparatively small vesicles exist; these are lined by a single layer of cubical epithelium, and contain colloid. At both the upper and lower end are collections of inflammatory cells. Throughout the whole of the anterior lobe the epithelial masses contain numerous swollen cells much larger than the normal epithelium, a large proportion of which are in a state of excessive vacuolation, and many are breaking down. Colloid spherules are in great abundance all over the glandular portion of the pituitary, but especially so along its anterior and upper borders. They are scattered irregularly amongst the cells within the alveolar spaces, or form distinct vesicles with a single layer of epithelium around. This colloid stains more deeply than that in the vesicles of the boundary zone. The stroma is fine and delicate for the most part, but here and there are strands of dense tissue. In parts the capillaries are engorged with blood; some contain colloid amongst the red discs. Many lymphatics are also distended with the same material. The peduncle is unusually thick; small vesicles containing colloid extend a long way up it, and exist in the capsule both above the anterior and posterior lobe. Long lymph-channels filled with colloid extend up the entire length of the peduncle. The posterior lobe is composed of loose connective tissue with intervening spaces filled with granular matter. In parts spindle-shaped cells are filled with brown pigmentary particles.

Thyroid gland.—The part chosen for examination contains a firm nodule as large as a pea. The section of tissue measuring one inch by half an inch contains this nodule, divided into deep staining cellular areas by fainter connective-tissue bands, such as entirely surrounds it. The connective tissue that has replaced the vesicular structure is partly of a loose œdematous nature, and partly dense and hyaline, and contains few nuclei. It is pierced by vascular spaces and clefts of variable size, some of which, having no appreciable walls of their own, are filled with a mucus-

like deposit, and probably belong to the lymphatic system; others are thin-walled veins. The smaller arteries present great thickening of their walls, but the larger ones are less affected, though some of the latter exhibit localised thickening.

The more deeply staining areas have taken the logwood tint indifferently. They are composed of compact masses of intermingled epithelial and lymphoid cells, all more or less in a state of degeneration. They are pierced by small arteries with greatly thickened walls, and contain numerous engorged capillaries. Extensive blood extravasation exists throughout these areas, which has caused them to assume a brown colour. There is scarcely any evidence of the normal vesicular formation of the thyroid to be found throughout the section. Scattered about the connective tissue are smaller deeply staining foci, due to an infiltration of the tissue with small round cells.

A lymphatic gland on the outskirts of the section is in a state of degeneration; the centre is occupied by loose myxomatous connective tissue; the lymphoid cells around are compressed and stain badly as a result of mucoid degeneration.

May 29th, 1900.

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40. *Absence of web in the feet of a duck.*

By E. A. Saunders.

The bird was a tame white duck (*Anas boschas* var. *domestica*, ♀) of a mixed breed of the Aylesbury and Pekin strains, and was bred at Laleham-on-Thames in Middlesex.

The deformity was congenital, and, though the breeder had reared ducks for many years, had occurred in this member only of the breed.

With the exception of the feet there was no abnormality. The length and the position of the toes were also normal. There was, however, some deformity of the toes, probably acquired, their extremities having a worn, thickened, and clumsy appearance, while the nails were cracked and distorted. This was most marked in the case of the inner toes.

The web was represented by a small basal portion in the angles between the toes (about 10 mm. in length from the angle

FIG. 4.

to the free edge of the web) and by a few scales along the sides of the toes themselves. These scales were not evident on the outer side of the middle toe in either foot.

The rudimentary portions of the web presented larger scales

on the dorsal aspect, and lesser scales on the plantar, as in the normal foot.

The duck was able to swim, though somewhat indifferently.

I have been able to find but two reported cases of this deformity: (*a*) one by F. O. Morris in the 'Zoologist,' vol. iv (1846), p. 1214; (*b*) one by Mobius in the 'Transactions' of the Zoological Society at Frankfort-on-Main, vol. xviii (1877), p. 223. Both these cases occurred in the male bird.

In (*a*), a Yorkshire-bred bird, the feet are described as being "to all appearance those of a common barn-door fowl." This bird is said to have swum "at the head of his progeny with much force and adroitness."

In (*b*), a bird bred in Germany, the rudimentary webs are described as being also 10 mm. in length. Here, again, the bird is likened to a duck with hen's feet, and the author mentions that a conjecture arose as to whether the mother had perchance paired with a cock. He goes on to say that as there has hitherto been no case recorded of a fruitful union between ducks and barn-door fowls, this view cannot serve as an explanation.

This bird is stated to have gone in the water with the others, though much less often. It is also said to have made the ordinary swimming movements, but to have progressed slowly. It was unable to dive.

With regard to the cause of this variation, it is difficult to say much. Although many instances of defect affecting the extremities, especially the ends of the extremities, are inherited in a marked degree, there is no evidence of any such tendency here. Nor is there sufficient reason to explain the occurrence of the deformity as a case of atavism, attributing the absence of the web to reversion to some primitive webless type.

It is, again, no great advance to find its explanation in a deficiency in hereditary endowment, or to seek satisfaction in the view that it is a failure in development of the germinal matter from which the web arises.

It should be mentioned that in the instance here reported, the breed of ducks had, as a matter of fact, been kept almost without opportunities of swimming, having only a small, shallow basin some six feet wide in which to splash about.

This had suggested the possibility of the disappearance of the web being due here to "disuse." However, if this were the

cause, we should expect a slow and gradual disappearance of the web in successive generations rather than the occurrence of the deformity in so sudden and complete a manner. In the other two cases cited, moreover, the birds appear to have had free access to water.

It is interesting to observe that the rudimentary web in two cases out of the three was approximately the same length, 10 mm.

At present the deformity can only be regarded as a case of "variation with loss," the loss in these cases having a tendency to be not only definite in character, but also apparently in degree.

The causes which underlie the occurrence of this variation are as yet unknown. *May 15th*, 1900.

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41. *Some anatomical rarities.*

By Samuel G. Shattock.

(With Pl. IX.)

It may be asserted that the specimens of highest interest in morbid anatomy are such as bear upon the problems of pathogenesis, whilst those possessing the least are such as partake only of rareness or curiosity. The small group described in this communication fall, as I have indicated by the title, into the second category.

(A) *Rupture of the tendons of the flexor profundus digitorum in a chimpanzee.*

This curious condition was found during the systematic dissection of a chimpanzee, lately carried out at the College of Surgeons for the purpose of illustrating the myological series in the Museum. The animal had been beyond recollection amongst the stores, so that nothing as to its history is forthcoming.

The specimen consists of the right hand and forearm.

The tendons of the flexor profundus digitorum have been

ruptured near their insertions into the terminal phalanges, in connection with which short portions remain. The other ends have been retracted as far as the bases of the digits, and are smoothly rounded, like the free extremity of a semilunar fibro-cartilage which has been for some time partially detached.

The tendon of the index is tied in a knot around the unruptured tendon of the flexor sublimis, after having been completely withdrawn through the perforation in the latter. This remarkable disposition is exactly that found during the dissection. The opposite hand presented nothing of the same kind.

Rupture of the tendons of the flexor profundus digitorum is an accident unrecorded in the human subject, and its occurrence in the chimpanzee must be associated with the habits of life peculiar to this animal.

It can hardly be wrong to suppose that the injury resulted during the animal's aërial gymnastics, from a violent contraction of the muscle made to save a fall whilst the terminal phalanges of one hand alone supported the weight of the body. If the accident were ever to arise in the human subject, it would probably be under analogous circumstances.

Knotting of the umbilical cord and of Meckel's diverticulum are well-known phenomena, but that of a ruptured tendon is unique.

The accident is an illustration of the part played by function in determining particular injuries,—a subject related to the influence of anatomical disposition in the causation of comparative fractures and dislocations, to which attention has been directed by Mr. E. M. Corner ('Lancet,' Oct. 1st, 1898, and Jan. 7th, 1899; and 'The Veterinarian,' Jan., Feb., March, 1899).

One of the most interesting examples adduced by Mr. Corner is the comminuted fracture of the sesamoid bones which lie in the flexor tendons behind the metacarpo-phalangeal and metatarso-phalangeal joints of the horse. Each of these joints is normally hyper-extended. As the animal gallops (explains Mr. Corner), a violent strain will be thrown on the flexor tendons and the sesamoids each time the legs reach the ground. As the sesamoid bones lie directly over the joint, the lower end of the metacarpal or metatarsal bone will be driven upon them with an action somewhat like that of a hammer. A predisposing cause of

this highly comminuted fracture is atrophy of the sesamoid bones arising from a previous want of exercise.

(B) *Unilateral synostosis of the temporo-maxillary articulation, preceded by an unusual amount of destruction of the jaw.*

Synostosis of the temporo-maxillary articulation is not so very uncommon a lesion as to require record, but in the present instance this has been preceded by so remarkable an amount of destruction of the jaw as to render the specimen one of anatomical interest; it has no other, for nothing whatever is known of the patient's history. The skull was exhumed at Benin City, and purchased by the College of Surgeons; the right half of the lower jaw is wanting. I have thus described it in the College

FIG. 5.

Showing synostosis following unusually extensive destruction of the temporo-maxillary articulation.

Catalogue:—"A skull, on the left side of which the whole of the condyle and neck of the lower jaw with the adjoining part of the ramus have been destroyed by a disease similar in its results to osteo-arthritis. The destruction has been accompanied with a considerable increase in the articulating area, not only in the antero-posterior, but also in the transverse direction; in the latter direction the articulating surface has a diameter of 2·3 cm. (nine tenths of an inch); in the former 3 cm. (one and three tenths of an inch). Except at the lowest or posterior part, the enlargement of the jaw articulates by suture with the apposed surface of the temporal bone; in the position excepted complete synostosis has occurred.

"The glenoid cavity has not been materially deepened, nor is there any deformity within the skull. The articular area has been extended anteriorly over the adjoining surface of the temporal bone almost as far as the greater wing of the sphenoid. As a result of the destruction, considerable displacement of the jaw has occurred towards the diseased side, the symphysis lying obliquely to the left of the middle line. The glenoid cavity on the opposite side is normal. There are no marks of osteo-arthritis on the occipital condyles."

The extensive destruction of the bone and accompanying peripheral enlargement, place the disease, of course, in the category of osteo-arthritis, more particularly the form associated with tabes. Certain of the cases of temporo-maxillary disease thus designated, however, present a feature in which they differ so remarkably from osteo-arthritis as observed in other joints, that it becomes questionable whether they should be regarded as uncomplicated examples of the same class.

There is not only in these an increase in the articulating area, due to circumferential outgrowth, but in place of destruction there is an accompanying elongation of the bone.

Robert Adams, in his monograph on 'Chronic Rheumatic Arthritis,' Dublin, 1857, has, under the temporo-maxillary articulation, so fully dealt with this subject, that little further remains to be said.

It is remarkable that in the first case of rheumatoid arthritis of the temporo-maxillary articulation observed by Adams (1836), this particular elongation of the affected bone was highly pronounced.

Since this observation of Adams's, one almost identical has been furnished by a specimen in the College Museum, No. 2205, which was presented by Mr. Jeremiah MacCarthy, and was described by Mr. F. S. Eve in the thirty-fourth volume of the Society's 'Transactions.' It would be difficult to find two preparations more alike. The jaw was taken from the body of a man forty years of age, who died of apoplexy; on inquiry it was stated that nothing had been noticed about his mouth as a child; there was no history of injury. The left half of the jaw in this specimen is smaller in all its dimensions than the right.

The articulating area of the diseased condyle is much increased (about four times); its surface is lowly and coarsely nodular; its margin, undulatory or crenate.

To these two cases must probably be added that recorded by Mr. Christopher Heath and Mr. Victor Horsley in the same volume, of a woman aged thirty-six, in whom during life the chin was displaced to the right side from enlargement of the ascending ramus on the left. In this case the left temporo-maxillary articulation was enlarged, but there was no ankylosis. In Mr. Heath's case the data are necessarily incomplete, since the part of the jaw examined was limited to that removed, and it is impossible to be sure upon the presence or absence of hypertrophy of the body itself.

The hypertrophic elongation of the bone accompanying the circumferential growth in these different cases renders them altogether unlike those of osteo-arthritis as it is seen in other joints.

In certain of the hyperplastic forms of osteo-arthritis, there are epi-articular as well as peri-articular growths, but these are of insignificant dimensions, and the disease of the bone is limited to its articular end; I have referred to such in the fortieth volume (p. 256) of the Society's 'Transactions.' It cannot be that osteo-arthritis of the temporo-maxillary articulation for some special reason entails hypertrophy of the bone, seeing that destruction and not elongation is so much the more frequent that it may be regarded as the rule.

It is not in the destruction, in fact, but in the amount of it, that the present specimen is unusual.

When Adams wrote, the particular form of arthropathy associated by Charcot with tabes had not, of course, been differen-

tiated. If we turn to Charcot's own observations it is interesting to find that the temporo-maxillary articulation was involved in the classical case of tabetic arthropathy described by him ('Œuvres complètes,' vol. ii, Appendix). The skeleton of this woman (of whom there is a life-size model in the Museum of St. Thomas's Hospital) presented articular lesions in the shoulders, the right hip, the knees, and the right temporo-maxillary articulation. For some days before her death, which occurred in December, 1876, the patient had felt crackings in the temporo-maxillary joint, the play of which was exaggerated. In the photographs of the bones in my possession the lower jaw is fortunately included, for it is not reproduced in Charcot's works. The jaw is edentulous; the left condyle is unaltered in form; the right, together with its neck, have been destroyed to the level of the sigmoid notch, but there is a prominent formation of new bone, and a corresponding extension of the articulating surface, on the inner side.

Even were the race of the skull exhibited determinable, its historic age would not be so; otherwise the question might be raised as to the evidence it offered of the antiquity and geographical distribution of syphilis, assuming that tabes is a sequel of this disease.

The present specimen is less remarkable for the synostosis that has occurred, than for the amount of destruction. Nevertheless synostosis as a sequel of osteo-arthritis in general is so uncommon, that Adams (*loc. cit.*) had himself verified by *post-mortem* examination only one example, the bones concerned being certain of those of the carpus.

In a specimen of temporo-maxillary disease (No. 1022) in University College, there is a partial synostosis; the jaws were sufficiently apart to admit of the patient being fed with a spoon. But a skull in the College of Surgeons Museum (No. 1949) shows synostosis that is complete. The articulating area on the left side is increased in width, that of synostosis (as shown by the section) being of corresponding extent; the circumferential enlargement of the articular portion of the jaw is confined to the inner side, where it is moulded upon the adjacent portion of the sphenoid; the opposite articulation is affected, though not ankylosed; there is no deviation of the symphysis from the middle line. Preparation No. 664 in the

Museum of St. Bartholomew's is, I think, an example of the same kind, in which the lower jaw has been forcibly divorced from the temporal bone after synostosis.

Cruveilhier ('Anatomie pathologique') records two examples of synostosis of the temporo-maxillary articulation. In one the condition was of rheumatic origin; the ætiology of the other is obscure. In the first, both articulations were synostosed, that of the left side completely, that of the right for the inner part only. The patient was affected after bivouacking on damp ground, the articulations of the lower extremities, then those of the upper, becoming the seats of pain, to which a clinical "ankylosis" succeeded. Feeding was carried out by removal of the upper central incisor teeth; articulation was distinct notwithstanding the immobility of the jaw.

In the other case, which is accompanied with an excellent figure (livraison 9, pl. v), the patient when eight years of age fell on her face and broke several teeth; after this she was unable to open her mouth; death did not occur until the age of fifty-nine. Articulation was unaffected. After death complete synostosis was found on the right side.

Synostosis of this articulation is not, it need hardly be said, in every case a sequel of osteo-arthritis; it may follow destruction arising from acute suppurative inflammation. In the latter circumstances the circumferential extensions of the articulating surfaces would, as in the case of other joints, be wanting.

(c) *A misshapen Elephant's tusk.*

[With Plate IX.]

The third specimen, I may notice, is one of the permanent incisor tusks of an African elephant, which presents near the junction of its posterior and middle thirds a sharp angular curvature of about 52 degrees. The length of the tusk as taken along its abnormal curvature is about twenty-four inches.

No part of the surface, except the pointed apex, is of natural contour. The surface in general is lowly tuberose, though not wanting in smoothness of detail, or density.

In addition to this primary character, it presents nummular elevations of varying extent, the surfaces of which are themselves

lowly tuberculated, and the margins of which are in places unattached so as to slightly overhang or overlap the parts beneath. The most noticeable change, however, consists in an extensive, yet generally smooth, depression, which commences somewhat abruptly at a distance of four inches in front of the angular curvature and anteriorly rises by imperceptible degrees to regain the general contour of the apex of the tusk. This depression has, in parts of its lateral extent, a sharp overlapping edge, the under side of which (like certain areas of the depression itself) bears minute hemispherical eminences. The base of the tusk in place of being hollowed, as it normally should be for the reception of the pulp, is almost filled in with an irregular dense formation, similar in general aspect to the substance elsewhere. The surface defect indicates a carious destruction of what may be named extrinsic origin, *i. e.* as arising from an alveolar periostitis and not from a primary disease of the ivory itself.

The depressed areas are smoothly healed, though over them are scattered a certain number of small nodules produced upon the healed surface from the alveolar periosteum. In other situations the alveolar inflammation has led to tuberculated and nummular formations over portions of the surface which have not apparently been at any time affected with caries, seeing that they present no alteration in general contour.

Whilst caries is in progress the surface of a tusk presents the depressed and eroded character of carious bone.

Amongst the diseased tusks, in the College collection, No. 2141 exhibits superficial caries in active progress, and accompanied in certain situations with nodular and nummular formations upon areas otherwise unaffected; in certain places it is clear that the caries involves areas upon which deposition has previously taken place, for the surface exhibits nodulated eminences which are in process of erosion: in yet other situations the depressed areas are smoothly healed, and upon such, new-formed nodules occur similar to those elsewhere.

Tomes, in his 'Dental Anatomy' (p. 374), states that the surfaces of the tusks in the females of the elephant are often deeply excavated, about the level of the edge of the gum, and are sometimes so weakened from this cause that they break off.

It must be remembered that in the normal growth of such a

DESCRIPTION OF PLATE IX.

Illustrating Mr. S. G. Shattock's communication on Some Anatomical Rarities. (Page 277.)

The elephant's tusk described in the communication, showing an angular curvature near the junction of its posterior and middle thirds.

The surface is in different degrees eroded by caries of extrinsic origin, and in places presents small nummular elevations of new-formed cement.

tusk, whilst the main bulk, the dentine, is formed from the persistent pulp, the cement which invests the dentine is developed, as in the human subject, from the alveolar periosteum.

An extensive caries of such a tusk would be brought about by the inroads of the granulation tissue formed from the alveolar periosteum, and any subsequent healing of the surface would be effected by similar tissue: for when once the dentine has been formed around and from the pulp, no further external accessions to it are possible; the tusk is displaced forwards by the continued growth behind, but it cannot be increased from the outer aspect except by the production of cement from the alveolar periosteum. The absorption of such dense tissue from without is witnessed in the shedding of the small deciduous or milk tusks, the bases of which are removed by the time the tooth is shed, an event that takes place between the first and second year; this absorption is, of course, precisely like that which affects the fangs of the human temporary teeth.

Microscopic grindings of the nummular elevations overlapping the smooth areas of the bent tusk first referred to, show that these consist solely of bone or cement. This is continuous on its deep aspect with the proper investing cement, which is readily distinguishable by the circumferential disposition of its lamellæ and a corresponding parallelism of its series of lacunæ.

In magnitude, some of the elevations are quite equal to those seen on the exterior of the human skull, which in like manner overlap the subjacent surface: and as the latter are dignified by the name of osteomata, so may those on the tusk, or, *mutatis mutandis*, they are cementomata.

In addition to these external marks of chronic inflammation, the filling of the pulp cavity is another. In some cases the condition last named is associated with the infliction of a gunshot or other injury, but of this there is no evidence in the present specimen. The injury in such circumstances is doubtless followed by an infective inflammation of the injured pulp, for in other cases, as is well known, the lodgment of a bullet may produce no similar deleterious result: as explained by Owen ('Odontography,' pl. 146), the formation of dentine from the pulp and the elongation of the tusk may, after a localised formation of osteodentine round the foreign body, proceed quite normally, with the result that the body itself (whether bullet

or spear-head) comes at length to lie embedded in the substance of the ivory, far, perhaps, beyond the proximal or growing end of the tusk.

Now as to the explanation of the angular curvature shown in the specimen.

The various changes on its exterior mark the results of an alveolar inflammation, which may or may not have been accompanied with suppuration—the condition known to dental surgeons as pyorrhœa alveolaris.

As a consequence the tusk has become loosened and mobile in its socket, the wall of which, in the condition above referred to, undergoes a varying amount of absorption. The ill-supported tusk, of its sheer weight, has then undergone downward displacement, the pressure exercised by the displacement of its retained extremity hastening the absorption of the alveolus.

As the production of ivory has proceeded from the persistent pulp in the base, the deeper or growing end of the tusk, formed after the occurrence of the displacement, has been developed in the normal axis and with a proper upward inclination.

The abruptness of the curvature shows that the descent must have been somewhat rapid—possibly a traumatic displacement was superadded to that started by the loosening of the tusk from the alveolar inflammation. In the human subject traumatic curvature of the fang other than that which may be due to fracture is a well-recognised lesion. Although the term "dilaceration" in use to describe such an accident supposes an actual laceration of the pulp, a flexion of the latter would produce the same ultimate result.

The seat of such curvature arising from displacement of the calcified portion of a tooth upon the pulp will depend upon the stage of development at which the accident occurs; should this be before the formation of the fang the crown only will be displaced, and the fang being afterwards developed in the normal axis, the tooth will present a permanent curvature at the junction of the two.

Specimen No. 3136.Gb. in the College of Surgeons Museum exhibits what may with certainty be regarded as such a result, and of which I have ventured to introduce a figure.

It is a deformed permanent incisor, the crown of which is united at an obtuse angle with the fang; the temporary tooth

was accidentally knocked out when the child was three years old, and its successor presented itself in the shape shown.

FIG. 6.

A. B.

A. A permanent incisor showing an angular curvature due to partial displacement of the crown upon the growing pulp.
B. A canine tooth, the fang of which presents a double curvature, due probably to flexion of the growing pulp from overcrowding.

Should the displacement occur later in the stage of development it might involve any portion of the fang, seeing that the latter is produced progressively from the crown onwards.

Other curvatures of the fang arise from what may be called flexions of the pulp during the development of a tooth. And owing to the confined position in which supernumerary teeth grow, such curvatures are particularly marked amongst this class.

No. 2135F in the College museum is a group of examples. The curvature of a fang may be simple or complex.

It is less difficult to suppose such as the latter due to corresponding complex flexions of the pulp of a growing tooth than to the dilaceration of direct traumatism, since the latter supposition would entail a precise repetition of the violence first sustained—a very improbable event. One of the most curiously curved teeth in the College series is No. 2136F, of which a figure is given in the adjoining woodcut. It is an ill-developed (and therefore probably supernumerary) canine tooth, of which the fang describes the curves; one of these is at the neck with the convexity towards the lingual surface; the other, at the middle of the fang, has the convexity in the opposite direction.

Owen ('Odontography'), citing from the monograph of Corse ('Phil. Trans.,' 1799), notes that anomalous "varieties" in the direction of the tusks are occasionally seen in the (Indian) elephant; as where one tusk is horizontal, the other vertical. Such an anomaly, it may be surmised, is the result of a one-sided

alveolar periostitis, or of traumatic dilaceration, or both combined.

A certain mobility, again, in the tusk of the elephant, which has been regarded as normal, rests, it is to be remembered, upon observations made on animals in captivity; and it is by no means clear that such a condition is not due to the same alveolar inflammation, the lesion being induced by infective processes arising in the mouth, which the altered habits of life accompanying captivity would favour.

The loosening and altered position of a tusk arising from alveolar periostitis have, like dilaceration, their exact counterparts in the human subject, in whom the shedding of permanent teeth without caries is an occurrence well known to dental surgeons, and one of which I have had personal experience. Without any caries the fangs of a tooth may become completely laid bare by the absorption of the alveolus arising from a chronic alveolar periostitis accompanied with a variable amount of discharge (pyorrhœa alveolaris). Not only are the teeth loosened during the course of the disease, so as to become quite mobile, but, to make the likeness almost complete, a tooth may, after loss of its neighbours, undergo such displacement in extreme cases as to lie horizontally on the gum.

Were a human incisor furnished with a persistent pulp, the subsequent growth would be productive of an angular curvature of precisely the same kind as that exhibited in the elephant's tusk described in this communication.

(D) *Two specimens of umbilical calculi.*

The first of these is a small flattened oval concretion or calculus, about three fifths of an inch (1·5 cm.) in chief diameter, which was removed from the umbilical depression, and consists of closely packed squamous cells, with a certain number of hairs.

It came from a man æt. 23 (admitted into St. Thomas's Hospital under the care of Mr. F. C. Abbott), who had noticed a discharge from the umbilicus for eight weeks. The abdominal wall around was indurated and tender. Two days after admission the calculus was extracted. It was, in the recent state, the size of an almond, smooth on the surface, of somewhat firm consistence and yellow colour. The sinus and a "granu-

loma" which had formed at its margin rapidly afterwards disappeared.

The second example is a somewhat flattened oval concretion nearly an inch in chief diameter (2·5 cm.), which was removed from a similar position. From certain parts of its smooth and silvery exterior there project the ends of fine pale hairs, and it presents in section traces of lamination; in the centre there is a small piece of flocculent material, which microscopic examination shows to be cotton-fibre. The concretion, like the preceding, consists solely of closely compacted, flattened, and wrinkled

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Illustrating Dr. J. W. H. Eyre's note on the Neutralisation of Culture Media. (Page 283.)

FIG. 1. FIG. 2. FIG. 3.

FIG. 1.—Filtered nutrient gelatine, to which phenolphtalein has been added and 3·5 c.c. of $\frac{N}{10}$NaOH run in from the burette. The medium is still acid, as evidenced by the unaltered colour of the sample.

FIG. 2.—The same after the addition of 4 c.c. of $\frac{N}{10}$NaOH. The production of this faint rose-pink colour indicates that the "end-point," or neutral point to phenolphtalein, has been reached. If such a sample is cooled down to say 30° or 20° C. the colour will be found to become more distinct and decidedly deeper and brighter.

FIG. 3.—The same after the addition of 4·5 c.c. of $\frac{N}{10}$NaOH. If after the end-point is reached a further 0·5 c.c. $\frac{N}{10}$NaOH be added to the sample the deep colour shown in this figure will be obtained.

(This is the colour American bacteriologists work to.)

in its entirety during the division of the abdominal wall.

May 29th, 1900.

42. *The neutralisation of culture media.*

By J. W. H. EYRE.

[With Plate X.]

REFERRING to the important influence exercised by the reaction of the medium upon the growth of an organism cultivated

thereon, Dr. Eyre entered a plea for the adoption of media—broth, agar, and gelatine—of a definite standard reaction for ordinary laboratory use, similar to those now in vogue in America.

He then pointed out that litmus, the indicator in general use in this country, was totally unsuited for exact work, as it was not sufficiently sensitive to weak organic acids and acid phosphates, but that in phenolphtalein we possessed a sensitive and reliable indicator, and one moreover which gave a very sharp and definite "end-point."

After describing the methods adopted in his own laboratory to produce media of a standard reaction, Dr. Eyre gave the various steps in the neutralisation. Briefly the method is as follows:

Take 25 c.c. of hot (boiling) medium, add 0·5 c.c. of a 0·5 per cent. solution of phenolphtalein (in 50 per cent. alcohol), now run in $\frac{N}{10}$ NaOH from an accurately graduated burette until the neutral point, as indicated by the appearance of a delicate rose-pink colour, is reached. Read off from the burette the amount of $\frac{N}{10}$ NaOH solution required to neutralise the 25 c.c. of medium, and from this calculate the quantity of $\frac{N}{1}$ NaOH necessary to neutralise the media mass from which the sample was taken. Reduce the figure thus obtained by 1 c.c. per 100 c.c. of medium; this gives the amount of $\frac{N}{1}$ NaOH required in order to leave the finished medium still *acid to phenolphtalein to the extent of* 1 *per cent.*—the "standard" reaction which appears to be the most generally useful.

Dr. Eyre showed a series of flasks of agar and gelatine demonstrating the colour produced when the "end-point" or neutral point to phenolphtalein was reached, and showing the marked effect in increased colour production, of the addition of minute quantities of $\frac{N}{10}$ NaOH to the medium after that point had been determined, an effect which proved that it was hardly possible for even the most inexperienced worker to make a greater error than 0·5 per cent. when titrating with $\frac{N}{10}$ NaOH, and using phenolphtalein as the indicator. *June 30th*, 1900.

43. A DISCUSSION ON THE BLOOD IN DISEASE.

(*April 3rd and May 1st*, 1900.)

SIDNEY MARTIN, F.R.S.

THE changes which occur in the blood in disease are of great importance from a pathological as well as from a clinical point of view. Consisting as it does of plasma, red and white corpuscles, and blood-plates, the blood has from time immemorial been the subject of laborious research, both from the point of view of the phenomenon of coagulation and from the nature of the corpuscles. In disease, not only do the plasma and corpuscles show great changes, but we have a large number of known effects of bacteria, which have received much attention of late years. In the present communication the changes of the blood in disease will be considered under three headings:

1. Changes in coagulability.
2. Changes in the corpuscles, both red and white.
3. The presence of toxic substances, and the relation of the blood to infection.

In the short time at my disposal it is impossible to deal at all fully with any one of these points; and there are many speakers here who are more competent than I am to speak with authority upon them. My province is by way of introduction, to suggest the lines of the discussion which is to follow.

1. *Changes in coagulability in disease.*—The phenomenon of the coagulation of shed blood has received great attention from experimenters at all times, and the simple statement by Schmidt that the formation of fibrin was due to the interaction of the so-called fibrin ferment on fibrinogen does not make the whole matter clear; for it does not take into account the close relation

which exists between the formation of fibrin and the presence of lime salts. Among the many ways, for example, of preventing coagulation of blood, is the removal of the lime by adding sodium oxalate to blood as it is shed, in the proportion of 1 to 1000. In this way you get an oxalate plasma which clots only after a long period; but readily on the addition of calcium chloride, as in the formation of casein in milk. Therefore lime salts are essential in the formation of fibrin in the blood; so that the phenomenon of coagulation has been ascribed to the interaction of lime salts with one or other of the proteids present in the blood.

The subject has developed of late years by the study of the class of bodies which are called nucleo-proteids. These nucleo-proteids contain phosphorus, and are by digestion separated into a body called nuclein, and a proteid which is capable of digestion. They are widely distributed in the body and in the blood itself. They exist in the red and white corpuscles, in the blood-plates, and in the plasma.

Fibrin ferment is considered by Pekelhäring as a lime compound of a nucleo-proteid. These nucleo-proteids are the same bodies with which Wooldridge worked in his experiments on intra-vascular clotting. On the one hand they have some relation to the class of proteid bodies called globulins, and, on the other, to the albumoses which are products of digestion. Without it being quite clear as to what exactly happens during the formation of fibrin from the blood, the nucleo-proteids are an important class of the organic constituents of the body, especially of the cells, and not improbably play a great and important *rôle* in disease. Wooldridge showed that the intra-vascular injection of what he called tissue fibrinogens, which are really nucleo-proteids, caused a clotting of the blood in the vessels during life in the majority of instances, although in some cases no clotting occurred and the blood was more fluid than normal. Intra-vascular clotting was therefore produced in this case without any injury to the vessel wall; the injection of the substance inducing a change in the blood which led to the formation of fibrin. Similar intra-vascular clotting was produced by Pickering with his artificially prepared colloids, and also by snake venom. Intra-vascular clotting frequently occurs without disease of the vessel wall in cases of infection; but what actually happens in such circumstances is at present unknown. It may be that the toxic

substances produced by infective agents may liberate a certain amount of nucleo-proteid in the blood, and so produce coagulation. There is some evidence that during the growth of bacteria, fibrin may possibly be formed. In some experiments which were carried out with the colon bacillus by growing it in a serum which had been sterilised by filtering through a Chamberland filter, I found that in many instances the continued growth of the bacillus resulted in a clotting of the serum, which was at first quite limpid. The colon bacillus is one which has practically no digestive action, although it secretes a very powerful poison. Its power of coagulating serum may show that the thrombosis occurring in infective disease is due to the action of the infective agent itself, but further research is necessary before any light from this source can be thrown on the phenomenon of fibrin formation.

Increased fluidity of the blood is frequently observed in infective disease; and it may be produced artificially by many different substances. The most familiar instance is by the injection of a certain amount of albumoses into the circulation of the dog or cat; the blood remains fluid in such cases after withdrawal. Similar results, however, are not obtained in the rabbit. The peptone blood which is obtained by this means can be made to coagulate by passing carbonic acid through it, by diluting it with water, by adding calcium chloride, nucleo-proteids or lymph cells. Albumoses as such do not exist in the body, and do not remain any length of time in the circulation when injected. How exactly the injection of albumoses into the blood-stream produces a fluidity of blood is not yet explained, but similar results have been obtained by the injection of malt diastase, of emulsin, of extract of leech heads, and extract of crayfish muscle; and fluidity of the blood is observed in poisoning by abrus, and by some of the poisonous substances formed by bacteria.

2. *Changes in the corpuscles in disease.*—The number as well as the character of the red and white corpuscles in health varies between only small limits in adult life. Red corpuscles, which we will first consider, appear during development in the vessels before the white. They are mesoblastic in origin, and before birth they are formed inside the cells. During the growing period in adult life the red corpuscles are constantly being

formed, mainly from the red marrow. The erythroblasts which are there found are nucleated (often having two nuclei), tinged with hæmoglobin, and vary not only in size but in shape; some being round, some oval, and some pyriform. The variation in size, in shape, and in nucleation of the developing red corpuscle is of importance in consideration of the changes which are observed in the red discs in disease. The red discs are the seat of the growth of the malarial parasite, which causes the destruction of the affected corpuscle, but does not produce any marked change in the corpuscles unaffected; so that the changes here observed are different from the more generalised ones which have to be considered. The increase in the number of red discs is in some cases temporary, as when there is a concentration of blood, as in profuse discharges from the body; but it is noticeable that both in phosphorus and in carbonic oxide poisoning an increase in the number of discs has been observed. Nothing further need be said upon this point, as the changes in the red corpuscles which are associated with anæmia require fuller discussion. The conditions of the blood in anæmia are usually divided into two groups: primary anæmia, which includes chlorosis and the pernicious form; secondary or symptomatic anæmia, which results from previous or co-existing disease, such as infective febrile disease, malignant disease, chronic suppuration, dysentery, cirrhosis of the liver and kidney, intestinal parasites, and certain poisons, such as lead and arsenic.

The variations in the corpuscles which are met with in disease may be considered under variations in shape and size, and variations in structure. Variations in shape consist chiefly in a loss of the dumb-bell form, that is of the central cupping of the corpuscle, and in the discs becoming either oval or pear-shaped. In size we have small corpuscles called microcytes, and those larger than normal called macrocytes. Variations in structure consist chiefly in the presence of nuclei in the red corpuscle. Nuclei may exist in small corpuscles or in very large and deformed corpuscles, and may show signs of division and of degeneration. Vacuolation of the corpuscle is also frequently observed in profound anæmias. These changes in shape recall the different varieties of erythroblasts found in the normal red marrow. They are corpuscles which do not undergo a normal

transformation into the adult red disc, but when discharged into the blood undergo degeneration. They are to be considered therefore as examples of arrested development of the red corpuscle.

To return to the consideration of anæmias: in secondary anæmia there may be various degrees; in some, hæmoglobin alone is diminished; in a more advanced condition the hæmoglobin is diminished but without any marked diminution in the number of the red corpuscles. The latter show the changes both in shape and size which have been described previously; and with this change in shape, a loss of rouleaux formation occurs. These changes are observed in malignant disease, lead poisoning, and most of the other conditions previously enumerated. In other cases of secondary anæmia, both the hæmoglobin and the number of corpuscles are diminished; and in still other cases, in addition to these changes, nucleated red cells appear in the blood, which presents then much the same signs as are found in pernicious anæmia. In chlorosis the pale watery blood coagulates rapidly, and while showing only a slight diminution it may be in the number of red corpuscles, there is a great diminution in the amount of hæmoglobin. Changes in the shape of the cells occur, but not to any great extent, although undersized red cells are frequently seen. The colour index of the blood is always low, that is below 1. The pale watery blood of pernicious anæmia is very slow in coagulating; the red corpuscles show no rouleaux formation, and while greatly diminished in number, they show rather a higher percentage of colouring matter, so that the colour index of the blood is usually over 1. The red cells also show great changes in shape and size, and nucleated corpuscles are frequently observed. It is impossible to consider the changes of blood in pernicious anæmia without thinking of a condition of poisoning. Such a great change in the blood, involving deficient formation of corpuscles as well as destruction of the cells, cannot arise spontaneously, and appears more likely to be the result of some profound change induced by an intoxication of the body. What, exactly, this intoxication is, has not yet been clearly defined: but there are sources of chronic intoxication which are known, and which have to be considered as agents in the production of the disease. Such is the intoxication which is the result of bacteria in the alimentary tract,

both in the upper and lower parts; and there is some evidence to show that chronic intoxication from this source may be one of the agents in the production of pernicious anæmia.

Of the white corpuscles of disease there is but little time to speak. The full discussion of this important subject I must leave mainly to others. The normal variations in the number of white corpuscles is greater than that of the red, both according to age and according to the physiological processes of digestion and of pregnancy. In disease an increase in the number of leucocytes occurs in many different conditions, which may, however, be divided into two great classes, the first class including those cases which occur as the result of infective disease, of definite poisoning, such as gas poisoning, quinine, the action of salicylates, and of ether; and those that occur in the course of malignant disease. All infective disease does not lead, however, to leucocytosis; notable examples being typhoid, malaria, and tuberculosis. The second great group of cases occurs under the heading of leukæmia, with its two varieties of splenic myelogenous leukæmia and lymphatic leukæmia; in the former of which the great feature as regards the blood, besides the enormous increase in the number of white corpuscles, is the presence of myelocytes which are derived from the marrow, and which are not present in normal blood. In lymphatic leukæmia the increase of leucocytes is not so great; and in both conditions, at any rate in the early stages, no change in the red corpuscles is observed. Later on, however, nucleated corpuscles occur, and there is an anæmia developed. In both these forms, as well as in some other forms of anæmia without leukæmia, an enlargement of the spleen occurs, which I can only just mention; but the presence of an enlargement of the spleen is of interest, as indicating a possible toxic origin of these conditions.

3. *The effect of certain toxic substances in the blood.*—The effect of certain toxic substances in the blood has already been mentioned, and it is impossible to study many of the conditions under consideration without feeling that an explanation of their occurrence may be that of an intoxication of the body. Toxic substances not only have a general action which may lead to death of the body, but they have a specific action, selecting certain tissues and organs of the body for their special effect;

and may produce by their results not a sudden death but a gradual one, which may show itself in slow changes of form and composition of the cells of the body. A prolonged action, however, of toxic substances has to be taken into relation with a degree of resistance of the individual; so that in a resistent individual there may be signs of reaction to the effect of a poison, and this is more particularly seen in the effects which are noticed as the result of the injection into the body of the poisons of bacteria. In certain doses they may kill; in smaller and repeated doses, they lead in certain conditions to the formation of substances which are of two kinds: either simply inimical to the life of the bacterium or inimical both to the life of the bacterium and to the effects of its poison; that is antimicrobic and antitoxic. These are new substances in the blood, inasmuch as even if present under normal conditions they must exist only in extremely minute quantities.

C. S. SHERRINGTON, F.R.S.

I feel that the subject under discussion, although of such large scope, is one which should give us grand chemical data, and therefore I also feel that those particular aspects of the question that I am at all competent to deal with I ought not to touch on at any considerable length, because by doing so I shall be hindering rather than advancing the true object of our meeting.

With regard to the histology of normal and morbid blood, many of the features have been already dealt with by Prof. Martin, and that fact leaves me freer to put before you a few suggestions only. First and foremost there is the histology of the red blood-corpuscles. I suppose there is no cell in the body that we can say we know better, of course with all due modesty. The monotonous regularity and appearance of uniformity of these cells must surprise one. And, speaking broadly, there is no more general feature than the departure from that uniformity of appearance and shape of the red blood-corpuscle which characterises morbid blood. That leads us to reflect that although in normal blood these corpuscles have that monotonous regularity of appearance they cannot be really all alike; there must be great individual differences between the apparently similar cells. When we reflect that there is a constant process of

disintegration and renewal of these corpuscles, the evidence is very obvious that there is a large diurnal excretion of pigment which is undoubtedly derived from the respiratory hæmoglobin of these corpuscles, but that nevertheless the standard of the blood is maintained. We see the extraordinary rapidity of the renewal after severe hæmorrhage. Some of the corpuscles must be young, others senile, the latter no doubt on their way to the liver, spleen, and mesenteric lymphatic glands to be destroyed. One wonders whether the differences that are known to occur in the resistance of the individual corpuscles to the osmotic tension of the fluids in which they are bathed is any key to these differences. Prof. Hamburger has introduced the red blood-corpuscle as an index for examining the osmotic tension of various fluids, keeping his attention chiefly upon the important organic fluids of the body. I myself rather suspect that the most interesting part of his investigation consists really in the number of facts which have arisen from his observations, showing us the great individual differences in the red blood-corpuscles so used as indices. That is to say, we find that one corpuscle is destroyed, disintegrated, at a very different degree of dilution from its neighbour in the very same specimen of blood. It is interesting that the nucleated red blood-corpuscles in those lower animals which have such corpuscles and no other, have a much greater resistance than the non-nucleated corpuscles in some of the mammalia; and the inference is suggested that perhaps those corpuscles which are the most resistent are those which are really the younger. What the normal mode of destruction of the red corpuscle in the body is, must, I suppose, still be regarded as a mystery. We know that the normal blood has never yielded in its plasma any reliable evidence of contained hæmoglobin; there is no trace of dissolved hæmoglobin in normal blood-plasma. That, I suppose, may suggest that all this daily continual destruction of red blood-corpuscles which must be going on, is perhaps carried out in an intra-cellular manner; that is, the worn-out corpuscle is eaten by some phagocyte in the appropriate organs for blood destruction, and in that way its hæmoglobin is not allowed, when the life of the corpuscle ends, to escape into the plasma. But that can hardly be the case in many diseases. One of course remembers paroxysmal hæmoglobinuria and black-water fever, in which a large amount of

respiratory pigment suddenly escapes and is excreted by the kidney. Then in malarial paroxysms the red blood-corpuscle, after the ripening of the intra-cellular parasite, is broken up, but we get, I think, no evidence that the hæmoglobin is excreted immediately from the body. I am told by Major Ross, who has examined a great deal the characters of the blood in acute malaria, that the destruction of corpuscles which goes on at that time is far greater than could be accounted for by the disappearance of only those corpuscles containing the parasite. That is to say, he feels very firmly convinced that there is an elaboration of some toxine at that time which leads to the destruction of other red corpuscles than those in which the parasites happen to ripen. In all these cases it does seem to me that observations, if we had them, upon the resistance of the red blood-corpuscle might be interesting, and might yield valuable information. I looked in vain for records of observations of that kind, such as Hamburger would describe as observations by which the osmotic tension of red blood-corpuscles is estimated. It might be supposed that under these conditions the corpuscle was less able to resist the disintegration that the osmotic force to which it was exposed would naturally bring about, and in that way the standard might be departed from which we know is so well and so admirably upheld by the normal living corpuscle, namely, that of maintaining its own osmotic tension when surrounded by plasma. v. Lunbeck has examined the tonicity of the corpuscle in a certain number of cases of anæmia, and he has found it altered. That apparently stands as an isolated observation of the kind. One would think that such an examination of the red blood-corpuscles might go hand in hand with observations upon the osmotic tension of the plasma in which they are immersed, and especially upon the alkalinity of the plasma. In spite of the evidence of Prof. Wright and others, it does seem desirable to ascertain this alkalinity by some more favourable and practicable method, if I may throw the suggestion out.

As to the leucocytes, so much attention has been paid to these in recent years, that an epitome of what is known about them is certainly unnecessary here, and is difficult to undertake. But we may congratulate ourselves, I think, on some of the results of the past fifteen years of work. One valuable result is a more natural classification of their different kinds. We owe that

especially to the late Prof. Kanthack, whose classification of leucocytes has certainly now been very widely adopted, and seems likely to be a permanent contribution and a standard for work upon the hæmic leucocytes for many years to come. The classification he adopted was into the finely granular or polymorphic nucleated leucocyte, the most common and characteristic of all blood leucocytes; and the coarsely granular oxyphil leucocyte, the typical eosinophil cell. The second is a far rarer form of the leucocytes present in normal human blood, endowed with different properties, and different indeed in every respect. The finely granular is a well-proved and active phagocyte, capable of marked amœboid movements; not apparently undergoing rapid changes in its granular appearance,—that is to say, yielding no definite evidence that it has secretory powers with regard to these granules. On the other hand, the rarer, coarser granular variety is very actively amœboid under certain circumstances, and yet has only dubitable powers, powers denied altogether by some observers, of phagocytosis.

I think Prof. Kanthack and those who worked with him never obtained observations which showed the possession by this coarsely granular leucocyte of the power of phagocytosis, of including bacterial or other cells. I certainly have never observed a single instance of that kind. On the other hand, Dr. Durham believes that he has seen it very rarely, and some French observers think they have done the same. Anyhow, it is a dubitable point.

Passing from these two leucocytes, we have a large hyaline cell, much more common than the coarsely granular leucocyte, and related in appearance to some of the marrow and spleen cells; an active phagocyte, but not very actively amœboid, in my experience. The possession of amœboid movements in these cells does not seem necessarily to carry with it the power of phagocytosis. There are, finally, the small lymphocyte and the basophil leucocyte, which last is the rarest of all the leucocytes that are denizens of normal blood.

After that classification, now so widely adopted, it seems to be thought necessary in making observations on the blood, not merely to count them, but to distinguish, to assort, to enumerate them in subdivisions. We owe to Dr. Phear, in a recent number of the Medico-Chirurgical Society's 'Transactions,' a paper that

seems to be very useful. It bases, on a very large series of observations, the approximate numbers of these leucocytes which should be present in normal blood. These numbers are rather different from those which have been previously accepted. The phagocytic forms, according to him, are fewer than had previously been thought. But, satisfactory as this knowledge is for the purpose of diagnosis, and the rapid recognition of different forms of leukæmia, and so on, one cannot help recognising that it does not take us much further than we were regarding the theory of the blood. There are yet a number of questions connected with these cells still unanswered. Where do they come from? What is the relation between the individual forms? Are they different species of cell, or are they different phases in the life history of one polymorphic individual? What is their normal use within the body? Professor Sidney Martin made valuable suggestions with regard to their uses as carriers of fat and glycogen. I think that no doubt they may perform these functions, but we should like to know a little more regarding the amounts they can move about the body, and the purpose and the means of their doing it. Without distrusting the existence of such functions, I must say that, on the whole, we are still very much in the dark even as to the nature of this granulation, and what its chemical characters are.

An old view concerning the function of the oxyphil granules related to the formation of hæmoglobin. I believe I am right in saying that the manner in which hæmoglobin is built up in the body is really unknown. There are two facts, however, that we do know with regard to the chemistry of the granulation in the coarsely granular oxyphil leucocyte, namely, that its granules are rich in phosphorus and iron. The iron is in organic combination, as tested by micro-chemical reactions, but beyond that I think we know very little. The observations of Kanthack and Hardy show that sudden changes appear in the granularity of the cells under their excitation in the neighbourhood of pathogenic organisms, and that remains the salient point gained. There is, of course, one aspect of the function of these leucocytes which I believe one is justified in thinking to be now much clearer than it was, namely, the attitude they bear to the process of inflammation. Without entering into any details concerning that process, I suppose it is justifiable to say that

the leucocytes may be looked upon as forces which can be drafted off to some tissue or site of irritation or injury, and that the phagocytic forms among them would there contribute to the process of inflammation by aiding phagocytosis, being themselves phagocytes; and that, accepting what we may call the humoral view, they will contribute substances of a defensive nature. Therefore may we not say that these hæmic leucocytes do not take any share themselves in the proper reparatory process? I speak now partly from impressions gained from the work of Mr. Ballance some years ago; I believe they do not really remain as permanent elements in tissue repair. Then, of course, there is a very general increase in the leucocytes of the blood, often preceded by a fall in their number, in cases of inflammation, even acute local inflammation, and this may be a very large increase. Experimentally, I have seen the number seven times the normal in twenty-four hours. But I think we are completely in the dark as to the theory of this great increase. We do not know whether the increase is due to the drafting of new corpuscles from elsewhere, or to an extremely active induction of those cells which are already in the blood. The cell most characteristic of all the hæmic leucocytes is the cell that is most increased under these circumstances, so that we might suppose that the great leucocytosis occurring is, in the main, due to an active reproduction of the blood-cell. At the same time this is difficult to harmonise with the fact that no clear evidence of any obvious amount of cell-division amongst the leucocytes in the blood is forthcoming. In examining leucocytes it is recognised that it is important, and usually easily practicable, to count the leucocytes in a living film (instead of in a dry, stained film), and in the same living specimen as that in which the red corpuscles are examined. That does seem to me a matter of some importance. It requires a great amount of experience and skill to get two minute amounts, drops of blood, exactly like one another. We can recognise in living films each one of these different cells, just as well as if they are dead and treated by differential stainings; and there are certain advantages that a living film has over a dry one, namely, that it is very easy to observe the amœboid powers of the cells, a matter of great importance, for example, in examining the blood of splenomedullary leukæmia. If the film be properly sealed with oil the

various characters are perfectly preserved for twenty-four hours, and even longer if kept in a cool room. A little methylene blue as Dr. Phear pointed out, adds very much to the recognition of the nuclei, since nuclei apparently take up this stain in the still living state.

As to the blood platelets, I suppose each of us has his view; there is great difference of opinion as to whether they should be considered cells or not. I feel very strongly that the blood platelets are not living elements of the blood at all, and I am completely in accord with the views of those who hold that they are rather of the nature of precipitates containing proteids, and perhaps many other things besides, shed either from the corpuscles or from the plasma of the blood itself. It seems to me that a direction in which this discussion might be useful is in criticism of the methods of examining the blood clinically, dividing them into those which are more useful and those which are less so. Any physiologist who looks at Dr. Copeman's article on the blood in Allbutt's 'System of Medicine' must be ashamed at the very meagre account that he will find in his text-books compared with the very full account in that "system,"—that is to say, the clinical methods seem to have got very much more numerous than those carried out in the physiological laboratory. The great distinction between the two sets of methods is that the great ingenuity by which the difficulties of examination by the "drop" method are obviated, enables it to be very practicable. Any criticisms or information which this discussion might produce would be very gratefully received by students and teachers of physiology throughout the country, because they feel that the time at the disposal of the student in the laboratory might be most usefully employed in gaining some dexterity and training in methods which can be made of actual clinical assistance.

One method which perhaps promises to come more and more into use is that of taking what is called a measurement of the double density of the blood; that is to say, a measurement of the specific gravity of the blood-plasma and corpuscles together, and afterwards a measurement of the density of the fluid of the blood-plasma. That can be so easily done by the centrifuge method, that in many cases a routine carrying out of such measurements might really be completed without serious loss of

time. As showing what importance such observations might have, one remembers that it has been shown how great the variations are in the total quantity of blood, even within short periods. In a severe or extensive operation, such especially as involves the opening of the abdominal cavity, or severe and acute local inflammations, there is a large and rapid alteration in the volume of blood. Those alterations in volume fall entirely upon the plasma. In one of the cases observed experimentally by Dr. Cobbett and Professor Roy, the volume of blood was reduced by one third within a few hours. As the loss falls upon the plasma, the density of the total blood is increased. I have seen it increased 20 per cent. within a few hours. That must be a matter of very considerable importance for the heart. When one recalls the fact that 99 per cent. of the work demanded of the heart is expended in overcoming the friction of the blood in moving on itself and overcoming the resistance in the peripheral circulation, the viscosity of the blood must be a matter of very great moment. No doubt the extreme instance of the effect of altered viscosity of the blood is to be seen in cholera, and especially on the lungs. From watching such cases one derives the impression that it is the inspissation which is overtaxing the mechanical power of the ventricles to move this thickened blood.

A. Wright (Netley)

understood that in the course of a discussion on the subject of the changes of blood in disease, they were not limited to discussing the very few facts which had been ascertained by the methods of blood examination already generally in use, but they had to take counsel together as to the methods by which they might obtain further information about the changes which took place in the blood in disease. The increase of knowledge on the question manifestly depended in large part on the introduction and exploitation of new methods of research.

In hospitals at the present time, the chief, and in many hospitals the only, method of blood examination which was in use was the hæmocytometric method, and this last was chiefly

directed to the enumeration of the red blood-corpuscles. In his opinion very little, if any, useful object was achieved by these enumerations of red blood-corpuscles.

A further method of blood examination which was indeed invaluable in cases where malaria was suspected (and it was capable of rendering great service also in the diagnosis of plague) was the method of microscopic examination of film preparations of the blood stained with a view to the disclosure of parasitic micro-organisms. The utility of this method was, however, confined to a very small class of cases.

A third, and more important method of examination, which was introduced by Professor Ehrlich, was the method of examining blood films, stained in a differential manner with the view to bringing out the character of the histological elements in the blood. This method often yields results of great importance. Conditions of simple anæmia can by it readily be distinguished from conditions of pernicious anæmia, not only by the poikilocytosis of the adult red blood-corpuscles which occurs in pernicious anæmia, but also, as Professor Ehrlich has pointed out, by the fact that megaloblasts are found in the blood.

Further, by means of the histological differences pointed out by Professor Ehrlich, the leucocytoses which are found in the incubation period of specific fevers and in association with ordinary inflammatory conditions can be differentiated from true leukæmic conditions. In the former class of leucocytoses the increased number of white blood-corpuscles as a whole, and in particular the increased percentage of polynuclear white blood-corpuscles, constitutes the characteristic feature; while in leukæmic conditions the characteristic features are, first, the increased percentage of the other varieties of white blood-corpuscles relatively to the polynuclear white blood-corpuscles; and secondly, the presence of abnormal forms of white blood-corpuscles, meaning thereby forms of white blood-corpuscles which are normally absent from the circulating blood.

In connection with the question of the varieties of white blood-corpuscles found in disease, the speaker referred to the opinion he had expressed that hæmophilia is associated with a small total of white blood-corpuscles and a very low percentage of polynuclear white blood-corpuscles. He had found these conditions in the blood of a large number of hæmophilic children

drawn from seven unrelated bleeder stocks. He had found the percentage of polynuclear white blood-corpuscles in a bleeder boy of eleven and a half years old as low as 35 per cent. The speaker had since, however, examined two adult hereditary bleeders who still suffered at intervals from the characteristic symptoms of the disease. The blood of these bleeders showed respectively percentages of 52 and 56 per cent. of polynuclear white blood-corpuscles. Doubt would appear to be cast by the last-mentioned observations and by the recently ascertained fact that the percentage of polynuclear white blood-corpuscles in the blood of children is much lower than it is in the adult, on the causal association of the hæmophilic diathesis with a very low percentage of polynuclear white blood-corpuscles. Nevertheless the speaker adhered in a modified form to the opinion that an unduly low percentage of polynuclears and an unduly small total of white blood-corpuscles stood in some causal relation with the hæmophilic diathesis; for he had found this character not only in many hæmophilic boys, but also in their maternal ascendants; and he had observed in one family where there was a sister and brother, both healthy and younger than the brother who suffered from bleeding, that the total number of white blood-corpuscles and the percentage of polynuclear white blood-corpuscles, were larger in these than in the older bleeder boy. While the bleeder boy, Willie, at the age of eleven and a half, had 7600 white blood-corpuscles with a percentage of 35 per cent. of polynuclears; his healthy sister, Maggie, at the age of nine, had 8600 white blood-corpuscles with 64 per cent. of polynuclears; and his healthy brother, Thomas, at the age of six, had 10,200 white blood-corpuscles with 55 per cent. of polynuclears.

After this excursus the speaker returned to the discussion of the methods of blood examination. In particular he called attention to the fact that the method of examining blood for the presence of agglutinins was generally exploited only for diagnostic uses. In his opinion the method was extremely valuable, also for prognostic purposes, and he referred to the fact that Courmont, of Lyons, in connection with typhoid fever, and Lamb and Birt (working in the speaker's laboratory with the method of quantitative determination devised by him) in connection with Malta fever, had shown the prognostic importance of a quanti-

tative determination of the agglutinins present in the blood. In particular Lamb and Birt had pointed out that the method was of great importance in enabling the occurrence of relapses to be predicted.

The speaker said that this completed the catalogue of methods of blood examination which were in current use, and he pointed out that it must be recognised that these methods revealed only a very few (and these perhaps not the most important) of the multiform changes which took place in the blood in disease.

A few words might therefore appropriately be devoted to some new methods of blood examination, which gave, he thought, information of considerable practical value.

The first of these methods he desired to draw attention to was the one he had described[1] for determining the coagulation time of blood. In this method blood from the finger was drawn up into a number of "coagulation tubes" of standard calibre; these last were kept at a standard temperature; they were tested by blowing down the successive tubes at different intervals in order to ascertain how soon after withdrawal coagulation became complete.

He considered that the information obtained by this method was of importance as furnishing an explanation of the pathology of various diseases. He had ascertained[2] by this method that the cause of the excessive bleeding in hæmophilic patients is invariably to be found in the diminution of the coagulability of the blood. He had, in several cases, seen the blood of hæmophilic patients remaining uncoagulated for more than an hour after it had been withdrawn from the finger under circumstances when normal blood would have coagulated in from three to six minutes.

He pointed out further that the excessive hæmorrhages which occurred from comparatively small wounds in the case of typhoid fever and phthisis are apparently associated with a diminished coagulability of the blood.

Again, it was ascertained by the speaker by means of the method just described that the coagulability of the blood was considerably reduced in the case of persons of a lymphatic habit

[1] 'Brit. Med. Journ.,' July 29th, 1893; February 3rd, 1894; 'Lancet,' August 1st, 1898.

[2] 'Brit. Med. Journ.,' July 14th, 1894.

of body (in particular in chlorotic girls), and further in the case of persons who suffered from chilblains and urticaria.[1]

He had also, as would be seen later on, found diminished coagulability associated with the œdema of Bright's disease.

The utility of the method was, however, not confined to the fact that it furnished an explanation of certain pathological symptoms; more important was the fact that by the method in question information could be obtained which was of importance in the treatment of these conditions. He pointed out that the therapeutics of aneurism, urticaria, chilblains, hæmophilic conditions, and all other conditions associated with diminished blood coagulability could only be elaborated on the basis of blood coagulation determinations made anterior to and subsequent to the adoption of certain methods of treatment.

Of facts of therapeutic importance which were of interest in this connection, he would briefly refer to the following.

Effect of presence of carbonic acid in the blood on blood coagulation.—It had been ascertained by the speaker by experiments[2] on the effect of the inhalation of carbonic acid, and further by other experiments which involved the production of a venous condition by the application of ligatures, that the presence of an increased quantity of carbonic acid in the blood had an important influence in increasing its coagulability.

He had applied the inhalation of CO_2 successfully in the treatment of epistaxis in the case of bleeders.

He further pointed out that the nocturnal incidence of urticaria and of spontaneous hæmorrhage in hæmophilic persons probably stood in connection with the fact that in sleep the output of carbonic acid was smaller than it was during the day.

The effect of alcohol on coagulability.—The speaker also pointed out that alcohol had a very considerable effect in diminishing blood coagulability.[3] He thought this was of great importance as showing that alcohol should never be exhibited in cases of actual or threatened bleeding, or in the cases of increased lymph transudation which he had, he thought conveniently, grouped together under the appellation of "serous hæmorrhages." He thought the fact that alcohol diminished

[1] 'Lancet,' January 18th, 1896; January 30th, 1897; September 19th, 1896.
[2] 'Brit. Med. Journ.,' July 14th, 1894.
[3] Ibid., July 14th, 1894.

blood coagulability also deserved to be borne in mind in connection with the treatment of phlebitis and all other conditions where spontaneous coagulation took place in the interior of blood vessels.

The excessive hæmorrhagic and serous effusion which follows on traumatisms in persons under the influence of alcohol affords a practical illustration of the influence of alcohol in reducing blood coagulability.

Effect of the restriction of fluid on blood coagulability.—The speaker had determined by the method spoken of above that the coagulability of the blood was greatly reduced when large quantities of fluid were ingested, and that the coagulability of the blood was increased when the intake of fluid was restricted.

The speaker thought an increase of coagulability similar to that which was obtained by the intake of fluid might possibly be achieved by the administration of hydragogue cathartics, and he thought it would be interesting to determine whether the good results which were obtained in the treatment of acute urticaria by the administration of magnesium sulphate might not be due to the withdrawal of water from the blood, and not merely to the removal of peccant material from the intestinal tract.

Restriction of the amount of food.—The speaker had observed in connection with the treatment of several cases of aneurism, and also in the case of experiments conducted on dogs, that the coagulability was diminished when the supply of food was restricted. He considered that this fact was of cardinal importance in connection with the treatment of aneurism. He thought that it clearly showed that the method of starvation ought to be abandoned as a method of treatment of aneurism, unless it could be shown by definite observations made with the coagulometer that a definite increase of coagulability was in the particular case actually achieved by the treatment. He thought that it would be found that an increase of coagulability could not be obtained by this method of treatment unless the process of starvation was carried to unjustifiable lengths.

Influence exerted on coagulability by the amount of lime salts in the blood.—The speaker pointed out that it was in consequence of observations on the actual increase of blood coagulability obtained by the exhibition of calcium chloride that he had recommended this drug as a useful one in the treatment not

only of hæmorrhage, but also of urticaria and chilblains, effusions into the subcutaneous tissue and into serous membranes and joints. He had also on the basis of similar observations recommended the administration of citric and other similar vegetable acids, in cases where the blood was unduly coagulable.[1]

In connection with the question of the administration of calcium chloride, he desired to point out that the drug is useful in two sets of conditions. It is naturally pre-eminently useful in conditions where the defect of coagulability is directly dependent upon a defect of the lime salts in the blood. It is also, but of course to a lesser degree, useful as a corrective of diminished coagulability in many conditions where the chief cause of the deficient coagulability is to be found elsewhere than in a defect in the lime salts of the blood. The justification for its employment in these last cases is to be found in the fact that the optimum of lime salts is only rarely present in the blood.

With a view to illustrating the importance of examining the coagulability of the blood, and of further investigating, when such diminution of coagulability has been found, the particular cause of the defect of coagulability, the speaker instanced the case of a medical man who suffered from urticaria. This urticaria appeared every day and on the very slightest provocation. He could not drink a glass of wine, or take a hot bath, or indulge in violent exercise without bringing out an urticarial eruption. Not only so, but the patient's condition was such that he could at pleasure bring out an urticarial rash over his arms and trunk by mere "force of will." The speaker had on two occasions seen the rash actually brought out before his eyes in the manner indicated, and the patient had informed him that he had often at school produced such an urticaria eruption in the manner indicated with a view to starting a "scarlatina scare."

Examination showed that in this case the blood coagulability was reduced; it was not, however, excessively reduced. The patient was then put upon a course of calcium chloride. The urticaria did not appreciably improve under this treatment. If, therefore, it can be assumed that the calcium chloride was here given in sufficient quantities, it would seem to be possible that this was a case where the optimum of lime salts was already present in the blood. Owing to the fact that the method which

[1] 'Brit. Med. Journ.,' July 14th, 1894.

is described below had not then been devised, this point was unfortunately not determined.

In view of the inefficacy of the calcium chloride in this case, search was made for some cause other than diminution of lime salts, which might explain the diminished coagulability of the blood. A cause for the defect of coagulability revealed itself on the microscopic examination of the patient's blood, the white blood-corpuscles in this case being less numerous than in normal blood, and the percentage of white blood-corpuscles being considerably reduced.

With a view to the correction of this condition, thymus tabloids (Burroughs & Wellcome's, twenty to thirty tabloids daily) were administered. As the result of this treatment, the white blood-corpuscles increased from a minimum of 4000 previous to the administration of the tabloids, to a maximum of 12,500, while the coagulation time of the blood diminished from a maximum of over ten and a half minutes before the exhibition of the tabloids to a minimum of five and a quarter minutes. Hand in hand with this went an improvement in the patient's condition with regard to his urticaria.

It may be mentioned as a point of interest that when the coagulability of the blood had been increased by this means, the patient was able to take alcohol and to indulge in hot baths without producing any urticaria. Further, the patient was no longer, by holding the appropriate mental image before his mind, able to evoke the urticarial eruption on his skin. This must obviously have been due, not to any loss in his power of determining by the means indicated a blood-stream to the superficies of his body, but to the fact that, owing to the increased viscosity of the blood, the determination of this blood-stream to the cutaneous vessels was no longer followed by any sensible increase in the transudation of lymph into the tissues of the skin.

In view of the fact that a single determination of the coagulability of the blood necessarily leaves unresolved the question as to whether calcium salts are deficient in the blood, and the further question as to how far the calcium chloride which is exhibited by the mouth is absorbed into the blood, the speaker set himself to devise a method by which the amount of lime salts present in the blood could be determined for clinical and experimental uses.

This could be done in a very simple manner by taking a series of capillary tubes filled in with oxalate of sodium solutions of graduated strengths, and by then adding to the oxalate of sodium solution contained in these tubes an equal volume of blood withdrawn from the finger tip. The method of filling the tubes and of mixing the contents is the same as that described by the speaker in connection with his methods[1] of testing, on the one hand, the agglutinating strength, and on the other hand, the alkalinity of samples of blood withdrawn from the finger. The tubes are placed in an upright position and the amount of lime salts in the blood is judged of by the strength of the solution which is required to keep the blood permanently liquid.

The method having been found, the first point that had to be ascertained was the strength of oxalate of sodium solution which will in ordinary conditions suffice to keep blood from coagulating. In a fairly extensive series of observations the minimum strength of oxalate of sodium solution, which was required to keep the blood liquid, was found to vary between 1 in 400 and 1 in 900. The average minimum strength of oxalate of sodium solution which suffices to keep the blood uncoagulated, lies in the midway between these extremes.

The experiments made by the speaker to determine (*a*) what amount of calcium chloride can be absorbed into the blood, (*b*) what is the optimum of lime salts in the blood, and lastly (*c*) what doses of the salt must be exhibited in order to obtain that optimum of lime in the blood, are still in an incomplete condition. Sufficient observations have, however, been made to establish that an actual increase of lime in the blood can be observed to occur as a result of the exhibition of calcium chloride by the mouth. In certain cases, however, very large doses have to be exhibited before a noticeable increase of calcium chloride in the blood comes under observation. Two of these will be incidentally referred to lower down. It will suffice here to note in this connection that the results of lime determinations in the blood, confirm the correctness of Dr. Savill's observation, that in cases of chronic urticaria where small doses have proved ineffectual, large doses of calcium chloride frequently afford the desired relief.

[1] 'Brit. Med. Journ.,' January 16th, 1897; 'Lancet,' March 6th, 1897; September 18th, 1897.

Of interest in connection with the determination of the amount of lime salts in the blood, is the fact that in two cases of ununited fracture, which were admitted into Netley Hospital during the last few years, the lime salts in the blood were found to be very much below the normal. The record of the first of these cases has unfortunately been lost; the other case when the patient came under observation, a solution of 1 in 900 of oxalate of soda sufficed to prevent coagulation of the blood. After the patient had been put upon a course of calcium chloride (15 grains t. i. d.), the minimum strength of oxalate of soda which sufficed to keep the blood liquid was a solution of 1 in 500.

In particular it would be interesting to examine the blood by this method in cases of urticaria which supervene on the one hand upon ingesting acid fruits and wines, and on the other hand upon the exhibition of soap enemas, for these urticarias are almost certainly associated with a defect of coagulability dependent upon a binding up of the lime salts in the form of insoluble combinations.

I cannot here fully enter into the grounds which seem to me to warrant this inference. Suffice it, in connection with the effect of eating acid fruit, that I have in a fairly numerous series of experiments obtained evidence of a diminution of coagulability after the administration of citric acid, and that I have in one case along with this diminution of coagulability seen slight but definite urticaria supervene. In connection with the effects of soap enemas I may perhaps be allowed to refer to the following experiment, which shows that a diminution of coagulability, and at the same time a diminution of the lime salts in the blood, may result from the absorption of soap from the large intestine.

Dog 20 *kilos. weight.*

June 1st, 1897, 2.15 p.m.—Coagulation time of blood (withdrawn from scratch on ear) 3 min. 45 sec.

Results obtained by mixing blood with its own volume of citrate of soda solution in capillary tubes. Blood mixed with—

2 per cent. solution of citrate of soda				.	.	Clot in twenty minutes.	
1·5	„	„	„	.	.	„	
1	„	„	„	.	.	„	„
0·5	„	„	„	.	.	„	„

2.30 p.m.—Four grammes of yellow soap introduced into the large intestine in 100 c.c. of water and retained.

3 p.m.—Coagulation time 4 min. 15 sec. Blood mixed with—

2 per cent. solution of citrate of soda			. .	Uncoagulated in 24 hours.
1·5	„	„	„ . .	Faint trace of clot.
1	„	„	„ . .	Tube accidentally broken.
0·5	„	„	„ . .	Firm clot.

3.30 p.m.—Coagulation time 4 min. 45 sec. Blood mixed with—

2 per cent. solution of citrate of soda			. .	Uncoagulated in 24 hours.
1·5	„	„	„ . .	„ „
1	„	„	„ . .	Traces of clot.
0·5	„	„	„ . .	Firm clot.

In connection with the importance of estimating the amount of lime salts in the blood the following interesting, but unfortunately very incomplete case may perhaps be considered. The patient in question, a private in a Hussar regiment, was taken ill on board a transport proceeding to South Africa with severe diarrhœa, which did not yield to any form of treatment. He was sent to hospital on arriving at the Cape, and was thence invalided to Netley. The diarrhœa continued throughout the return voyage. On arrival at Netley the patient was in a very reduced, anæmic condition. A few days after admission, the diarrhœa still continuing, the patient developed acute œdema of the legs. His urine was then found to be loaded with albumen, the albuminous precipitate amounting, on cooling, to more than half the volume of the urine.

On examination of the patient's blood the coagulability was found to be diminished, the coagulation time being 13¼ minutes. Specimens of his blood were examined microscopically and showed a diminished number of white corpuscles, and a somewhat diminished percentage (55 per cent.) of polynuclear white blood-corpuscles. The determination of the lime salts in the blood showed that admixture with the blood of an equal volume of a solution of 1 in 2000 of oxalate of soda sufficed to prevent coagulation. In view of this result calcium chloride was prescribed in thirty-grain doses, these being administered three times a day. Two days after the commencement of the treatment the minimum strength of the oxalate of soda solution which sufficed to keep the blood liquid was a solution of 1 in 1200. The

coagulation time was now 12 min. 10 sec. After two further days on the same treatment, the minimum strength of oxalate of soda which sufficed to keep the blood liquid was a solution of 1 in 900. The blood coagulation time was now 10 min. 45 sec.

After five further days of the treatment the œdema had quite disappeared, the diarrhœa had stopped, the quantity of albumen in the urine had diminished at the rate of an inch a day, as tested in Esbach's tube by the Civil Surgeon in subordinate charge. Owing to the pressure of other work it was not possible to make accurate determinations of the daily amount of albumen in the urine. The patient then left hospital.

An unexplained feature in this case was the fact that during the last period of five days in which the symptoms continued to improve the amount of lime salt in the blood and in correspondence with this, the blood coagulability, decreased. It is perhaps possible that this may have been due to the increased flow of urine which manifested itself in this last period, being accompanied with an increased excretion of lime salts.

Lastly, the speaker referred quite briefly to the method which he had suggested for measuring the alkalinity of the blood.[1]

In the method in question, the serum obtained from a small quantity of blood, which has been collected from the finger in a blood-capsule, is mixed in a capillary tube with an equal volume of an acid solution of known strength. Tested by this method the alkalinity of normal blood may conveniently be represented by the formula $\frac{N}{35}$. In other words, the alkalinity of the blood is normally such that it can be rendered just neutral to sensitive red litmus-paper by the addition of its own bulk of normal acid diluted thirty-five times.

That the alkalinity of the serum gives a true measure of the alkalinity of the blood was shown by the fact that the speaker had obtained identical values for the alkalinity of his own serum, of his own citrated plasma, and of his lymph, obtained from blisters raised by the application of heat, and also by the application of Spanish fly.

Another preliminary point with regard to the method which deserves attention is that no reduction of alkalinity comes under observation when the blood is kept *in vitro* in a sealed capsule

[1] 'Lancet,' September 18th, 1897.

as long as forty-eight hours after it has been drawn off. On the other hand, Major Leishman, R.A.M.C., working in conjunction with the speaker, had determined that a reduction of alkalinity frequently, if not always, takes place in the body after death. In one remarkable case where the alkalinity was already reduced before death, the serum obtained at the *post-mortem* was found by Major Leishman to be not only definitely but excessively acid.

In connection with the result obtained by his investigation of the alkalinity of the blood the speaker adverted to the fact that he had recently obtained by this method confirmation of the views as to the pathology of scurvy which had been formulated by him in a paper published in the 'Army Medical Report' for the year 1895 (published in March, 1897). It was pointed out in that paper that since the scorbutic dietary was a dietary in which there was an excess of mineral acids over bases, and inasmuch as an antiscorbutic dietary was a dietary in which the bases were in excess over the mineral acids, it seemed probable that the scorbutic condition was the condition of acid intoxication, and that the effect of the vegetable diet in curing scurvy was due to the fact that a dietary of this kind contributed to the correction of "acid intoxication."

The patients who are here in question had formed part of the beleaguered garrison of Ladysmith. They were recently admitted to Netley Hospital in an extremely reduced and, indeed, precarious condition, suffering from dysenteric symptoms. All of them presented a characteristic dark greenish-yellow complexion. One of them had in Ladysmith suffered from continual epistaxis. Another was still covered with the remains of purpuric spots, and showed some sponginess about the gums and ulceration under the tongue. The third case was complicated by advanced phthisis, associated with large cavities in the lungs.

During the siege of Ladysmith the patients had of necessity been on a scorbutic dietary, and since the relief of the town up to the date of examination all vegetables had according to the patients' statement been withheld from them for fear of aggravating the dysenteric symptoms. The alkalinity of these three patients' blood was represented by the formulæ of $\frac{N}{200}$, $\frac{N}{150}$, $\frac{N}{80}$.

In view of the blood findings the patients were placed upon a regimen of lactate of soda. After the administration of

120 grains of lactate of soda along with small quantities of bicarbonate of soda, given with a bismuth mixture, the alkalinity of these three patients' blood was represented by the formulæ of $\frac{N}{40}$, $\frac{N}{35}$, $\frac{N}{36}$ respectively.

The condition of the first two patients underwent immediate improvement, their colour soon becoming healthy, and their strength increasing, so that they were soon out of danger. The third patient succumbed within a few days to his tubercular affection.[1]

J. Lorrain Smith.[2]

The methods in ordinary use for examining the blood of patients suffering from anæmia fail to give any information whatever regarding the total quantity of blood in the circulation, or the total amount of hæmoglobin which it contains. In other words, we are without the means of discovering the relation which the capacity of the blood for oxygen bears to the amount of tissue which it has to supply.

It has recently been shown by Dr. Haldane and myself that the carbonic oxide method can be applied to the investigation of the blood of the human subject, so as to afford the information which is lacking on these points; and in the present investigation I have made a series of observations with the purpose of showing how far the different types of anæmia are characterised by abnormal values in the total volume and oxygen capacity of the blood.

A full description of the apparatus required for the application of the carbon monoxide method to the human subject is given in the paper by Dr. Haldane and myself in the 'Journal of Physiology,' vol. xxv, p. 331; I need, therefore, now give only a short summary of the argument. The patient respires a mixture of oxygen and air contained in a small india-rubber bag. That provided with a Clover's inhaler is very suitable. The oxygen is supplied from a cylinder, and should form the

Certain further cases of scurvy which came under observation subsequently to the date of the discussion are considered in a paper by the speaker published in the 'Lancet,' August 25th, 1900.

[2] The investigation embodied in this contribution to the discussion was carried out at the Pathological Laboratory, Queen's College, Belfast.

larger part of the contents of the bag. The carbonic acid which would accumulate is absorbed by soda lime so placed that the to-and-fro currents of respired gases are fully exposed to it. Into the bag by a side tube known quantities of carbon monoxide are introduced at intervals, and the patient, breathing the contents of the bag over and over again, gradually absorbs the whole of this gas into his blood. Oxygen is supplied from the cylinder as required. After the last c.c. of carbon monoxide has been introduced into the bag, the patient is allowed to continue breathing for a few minutes (usually four). This allows practically complete absorption of the gas to take place, as well as equal distribution of it in the circulating blood. A sample of blood is then taken by pricking the finger and receiving two or three drops into a small test-tube containing water. Sufficient to make about 10 c.c. of a 1 per cent. solution is the amount of blood required. The percentage of carboxyhæmoglobin present is then estimated by the carmine method.[1] We discover in this way, that after the absorption of a known amount of carbon monoxide there is a certain percentage of carboxyhæmoglobin in the whole blood, and it is simple from this to calculate how much carbon monoxide would be required to convert the whole of the hæmoglobin into carboxyhæmoglobin.

The amount of carbon monoxide which the blood would absorb in being saturated is the measure of the total capacity of the blood for oxygen, as well as for carbon monoxide, since hæmoglobin has the same capacity for both gases.

The question now arises, how shall we connect this measure of the oxygen capacity with the volume of the blood?

In the paper by Dr. Haldane and myself just referred to, we have described experiments to prove that the oxygen capacity of any given sample of blood can be accurately estimated by estimating the amount of hæmoglobin colour present in it. We therefore take a measured volume of the patient's blood (about ·05 c.c.), and estimate the colour of it by comparing it with an equal sample of ox blood, of which the capacity for oxygen per 100 c.c. has been determined, and we can from the results of the comparison calculate the capacity for oxygen in any given part of his blood. Since from the saturation by carbon monoxide we already know the total capacity of the blood, the

[1] 'Journal of Physiology,' xxii, p. 232.

total volume corresponding to the total capacity can be directly calculated. The argument may be stated in its simplest form as follows:

A patient having absorbed 100 c.c. of CO, it is found that his blood is 20 per cent. saturated by this gas. The total capacity for CO, and therefore for oxygen, is 500 c.c. The patient's blood is further found to have the same colour as an ox's blood, of which the capacity for oxygen is shown to be 20 volumes per cent. The volume of the patient's blood therefore is $\frac{500}{20} \times 100 = 2500$ c.c.

The oxygen capacity of a given volume of ox blood may be ascertained by the blood gas-pump, or by the potassium ferricyanide method described by Haldane. The latter method was used in the present research.

As regards the actual observation of a patient, there are practically no difficulties. The rule I have adopted is to administer a quantity of gas sufficient to saturate the blood about 20 per cent. This produces no appreciable effect on the patient as far as my experience goes, and I have now examined over 100 cases. I have also frequently been the subject of observation. As will be seen from the tables, the volume of gas required in cases of anæmia from hæmorrhage, or in pernicious anæmia, is much smaller than in the normal individual. The time required for an observation is 10 to 15 minutes.

The results which Dr. Haldane and I obtained from normal individuals showed that the total volume of the blood is much more variable than the total capacity for oxygen. We found that the average volume of blood is 4·6 c.c. per 100 grammes of body-weight (translated into weight, the blood is $\frac{1}{22}$ of the body-weight). The average oxygen capacity of the blood was 18·5 volumes per cent., while the ratio of the total capacity to body-weight gave an average of ·83 c.c. per 100 grammes of body-weight. The ratio of volume to body-weight was found, however, to vary as much as 28 per cent. from the mean, whilst the ratio of oxygen capacity to body-weight varied to about 13 per cent. This fact is of great interest in relation to the present research, since this physiological variation indicates a condition which explains a type of anæmia to be described below, in which the chief change in the blood is an increase in the volume, whilst the total capacity of the blood for oxygen re-

mains relatively normal. It will be shown that such a form of anæmia contrasts clearly with that due to actual deficiency in hæmoglobin.

The total capacity for oxygen is here taken to be a measure of the total amount of hæmoglobin present in the blood.

Chlorosis.

The theory of the nature of chlorosis which is current is based on percentage observations of the blood, the cubic millimetre being the unit of measurement. Arguing more or less explicitly from such data, it has been generally held that the essential change in the blood in this disease consists in a reduction in the amount of hæmoglobin below the normal value, with or without a reduction in the number of red corpuscles. The reduction of the number of red corpuscles being less than that of the hæmoglobin, each corpuscle is poorer than a normal one in hæmoglobin. The leucocytes are not as a rule much affected. There is, however, a tendency to increase of the proportion of lymphocytes.

These percentage observations, however, are not sufficient to support the theory when it is implicitly made applicable to the total amount of hæmoglobin and other constituents in the blood. In the tables of cases of chlorosis which follow the percentage, observations are given with estimations of the total volume of the blood, and its total capacity for oxygen—the latter value being, as I have said, the measure of the amount of hæmoglobin in the blood. The cases examined arrange themselves naturally into several groups. We may take, in the first place, a set of twenty-one cases in which the hæmoglobin per c.mm. was less than 50 per cent. of the normal.

TABLE I.—*Cases of Chlorosis with Hæmoglobin under* 50 *per cent. per c.mm.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
C. H., 18 years	32·6	8·0	408	35·6	6181	2·110	48·0	12·9	0·85
M. S., 20 years	52·1	11·4	448	37·8	6400	3·360	50·0	12·8	0·89
M. H., 22 years	71·7	14·7	487	42·1	6244	4·000	54·0	11·5	0·90
S. B., 17 years	67·6	20·0	338	34·6	5281	3·300	43·0	12·2	0·78
M. K., 19 years	65·3	22·2	323	40·0	4364	5·160	40·0	10·9	0·81
E. M., 17 years	67·6	22·7	298	47·0	3425	4·680	42·0	8·1	0·70
L. W., 19 years	75·4	23·5	320	35·1	4923	2·350	40·0	12·3	0·80
F. S., 16 years	68·8	17·6	390	48·3	4357	4·240	40·0	10·8	0·97
M. W., 21 years	68·3	21·4	319	33·5	5145	4·092	51·0	10·0	0·62
M. K., 17 years	67·7	18·0	376	32·4	6266	2·600	43·0	14·3	0·87
E. C., 18 years	79·5	23·2	342	40·0	4574	3·012	43·0	10·6	0·79
M. K., 26 years	73·4	19·3	380	40·0	3653	4·287	49·5	7·3	0·76
J. S., 18 years	77·5	28·0	277	29·1	5129	2·040	41·0	12·4	0·67
L. G., 21 years	66·7	22·4	297	38·3	4183	2·370	42·0	9·9	0·70
M. R., 19 years	70·2	19·2	365	34·0	5993	2·500	44·0	13·6	0·82
S. J. D., 18 years	52·0	18·3	284	50·0	3020	4·100	40·0	7·5	0·71
N. H., 17 years	69·3	21·0	330	49·0	3626	3·060	44·0	8·2	0·75
A. G., 17 years	67·2	18·0	373	47·0	4238	4·020	40·0	10·5	0·93
M. G., 19 years	69·0	22·1	312	35·0	4727	3·200	49·0	9·6	0·63
C. F., 20 years	67·2	11·9	547	47·0	6216	3·800	54·0	11·5	1·0
M. H., 19 years	68·4	21·0	327	44·0	4000	2·600	44·0	9·1	0·74
Average.....	—	—	359	39·9	4883	3·222	44·8	10·8	0·79

The first point which follows from this table, is that in the anæmia of chlorosis the volume of the blood is increased in proportion to the severity of the disease. At the same time it is clear that the total oxygen capacity or total amount of hæmoglobin is approximately normal. The average of the twenty-one cases in the table is just over 95 per cent. of the normal. The condition then may be described as consisting in a great increase in the plasma of the blood, the apparent loss in hæmoglobin being due almost entirely to the increase in plasma.

Various aspects of these observations call for further explanation, and in the first place it is important to note that it has been ascertained, by several observers, that the specific gravity of the plasma in chlorosis is the same as that of the normal blood. The increase in volume therefore arises from a surplus of normal plasma. In other words, the change in the plasma, so far as it is known, is a quantitative one merely. The cause of this change in the volume of plasma is altogether obscure. It suffices to remark now, that increase of the plasma occurs also, as we shall see, in forms of anæmia other than chlorosis.

In the next place, when we take into account the increase in volume, it is clear that there is a large increase in the absolute number of red and white corpuscles. We may consider the red corpuscles in the first instance. Let us take a marked case, *e. g.* that of M. K., No. 10 in the table. There are 2·60 millions of red corpuscles per c.mm. The total volume is 14·3 c.c. per 100 grammes of body-weight, *i. e.* over three times the normal amount. If we filtered off this excess of plasma, there would remain about eight millions of red corpuscles per c.mm. of the blood, with normal volume of 4·6 c.c. per 100 grammes. This increase is due either to an excessive formation, or to a diminished destruction of red corpuscles, and there is evidence of its existence during the progress of the disease, apparently from the beginning. Cabot points out ('Clinical Examination of the Blood,' p. 134) that in chlorosis the first change in the course of the disease is a loss of substance in the corpuscles, without diminution in number per c.mm. The diminution in number occurs later.

It results therefore that signs of the increase in the plasma, in the earlier stages of the disease, are hidden, so far as the cor-

puscles are concerned, by the increase in their number. Each one, however, contains less than the normal amount of hæmoglobin, and consequently the indication of the disease is the decrease in the percentage of hæmoglobin. It may be that the increase of corpuscles is an active effort at compensation in the presence of excessive plasma. Ehrlich points out that the breaking up of larger corpuscles into a series of smaller ones increases the respiratory surface of the mass. There is no such compensation in regard to the hæmoglobin per c.mm. Later, the compensation in corpuscles fails also.

The relation of the leucocytes to the increase in volume differs from that of the red corpuscles. It is generally agreed that there is very slight, if any, diminution in the number of leucocytes per c.mm. The leucocytes maintain their normal number only because they increase in direct proportion to the increase in plasma, and this is of interest in the interpretation of leucocytic immigration in general. In the case (No. 10) just considered, the reduction of the plasma to normal volume would leave 16,000 leucocytes per c.mm. It therefore becomes necessary to distinguish between a percentage, and an absolute, leucocytosis. The leucocytosis which has been observed to occur during the cure of chlorosis is to be accounted for by the concentration of the blood.

The behaviour of the leucocytes in relation to variation in volume is a subject which I am at present investigating. It is interesting to point out, however, that the differential enumeration of leucocytes in chlorotic blood shows an increase in the lymphocytes. According to Ehrlich, lymphocytosis is due to an increased flow of lymph washing the cells out of the lymphatic tissue in a simple mechanical fashion. We may, therefore, on this hypothesis, suppose that, not only is there an accumulation of fluid in the blood vessels in chlorosis, but there is also an increased quantity of lymph poured into the blood.

TABLE II.—*Cases of Chlorosis with Hæmoglobin over 50 per cent. per c.mm.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
M. B., 19 years	51·9	13·4	387	82·0	2528	4·412	49·0	5·1	0·79
S. C., 17 years	68·0	23·0	295	51·0	3105	3·340	48·0	6·4	0·61
P. B., 20 years	73·1	20·8	351	80·0	2387	5·400	47·0	5·0	0·74
M. W., 19 years	80·3	15·5	517	82·0	3379	3·600	58·0	5·8	0·89
E. G., 18 years	55·1	14·7	375	58·3	3472	3·600	40·0	8·6	0·93
M. M., 22 years	55·2	13·3	415	65·0	3401	3·175	50·0	6·8	0·83
L. T., 26 years	69·1	18·4	373	57·0	3518	3·915	48·0	7·3	0·78
Average.....	—	—	387	68·0	3113	3·920	49·0	6·4	0·79

This table includes a series of cases of less marked chlorosis. The hæmoglobin per c.mm. varies from 50 per cent. to 80 per cent. of the normal. Those cases which have 80 per cent. of the normal hæmoglobin can hardly be considered chlorotic at all; but I have included them for the purpose of showing that there is the same variation in oxygen capacity per 100 grammes of the body-weight as in the series of marked cases. The average is practically the same as in the former series.

TABLE III.—*Cases of Chlorosis of Long Standing.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
B. N., 20 years (5 years' illness)	70·8	27·6	256	23·6	5818	3·120	40·0	14·5	0·64
S. L., 19 years (3½ years' illness)	52·4	20·3	258	22·0	6292	2·050	50·0	12·5	0·51
Average.....	—	—	257	22·8	6050	2·585	45·0	13·5	0·57

I have placed separately these two cases in which there was evidence of long-standing disease. One of these I have examined on several occasions; but, so far, careful treatment has not produced any distinct benefit. The marked diminution seen here in the total amount of hæmoglobin suggests that such a result may arise when the condition is one of long-standing chlorosis. The average of these two cases gives a total of 68 per cent. of the normal. No evidence could be discovered that hæmorrhage in any form had occurred. It is impossible, however, to draw any definite conclusion from such a small number of cases, especially as two or three cases in the first table have a total of 75 per cent. of the normal hæmoglobin, and no special condition, such as long-standing disease, or hæmorrhage, could be given in explanation of them.

To be compared with these cases, I have included a table of cases which came to hospital suffering from some disease which does not specially lead to changes in the blood.

TABLE IV.—*Cases without Anæmia under Hospital Treatment.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.	
E. M. G., 26 years	66·4	12·9	514	120·0	2315	—	57·0	3·9	0·88	Chronic abscess.
M. S., 19 years	46·6	15·0	310	91·0	1887	3·980	44·5	4·2	0·69	Debility of uncertain origin.
J. McK., 15 years	41·4	13·5	304	77·0	2111	3·400	34·0	6·2	0·89	Purpura (mild).
G. B., 18 years	51·8	17·0	305	80·0	2060	5·120	42·0	4·9	0·73	Benign tumour.
A. K., 30 years	66·1	16·7	395	100·0	2101	6·930	48·0	4·3	0·82	Pleurisy.
Average...	—	—	365	93·0	2094	4·857	46·3	4·7	0·80	

The point of interest here is, that the average amount of hæmoglobin is practically that of the cases of chlorosis already discussed.

Another standard of comparison is to be found in the next

table, recording observations the subjects of which were lady medical students of the fourth and fifth year, who were working in the department.

TABLE V.—*Medical Students [female] of the 4th and 5th year.*

Name.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of haemoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of haemoglobin. Normal=100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
M. L.	110·4	19·5	566	98·0	3109	5·360	70·0	4·4	0·81
L. S. G.	110·4	21·6	511	90·0	3077	4·700	50·0	6·1	1·02
C. L. B.	109·8	16·9	649	93·0	3773	—	64·0	5·8	1·01
M. E. L.	103·5	17·5	591	93·0	3436	—	62·0	5·6	0·95
M. B. A.	102·7	22·3	460	98·0	2527	5·000	56·0	4·5	0·82
P. S. G.	103·5	24·6	420	87·0	2608	4·750	44·0	5·9	0·95
Average	—	—	533	93·0	3138	—	57·0	5·3	0·92
Average for males ..... ('Journ. of Physiol.,' xxv, 340)			599	100·0	3254	—	72·2	4·6	0·83

Here the average oxygen capacity per 100 grammes of body-weight is ·92. This is somewhat higher than the average of ·83 which Dr. Haldane and I found from observations on men. The question of deciding exactly what the normal standard should be must be left for further investigation.

Observations on chlorosis in general have been in relation to its cure rather than to the period of onset, and the successful treatment of chlorosis with salts of iron is a fact which has attracted great physiological interest. The usual interpretation of this is that there is a synthesis of hæmoglobin in the body from the salts of iron. From the tables it is clear that in typical cases the cure by iron may be complete without any increase in the total amount of hæmoglobin, and that consequently the recovery affords no ground for assuming that iron is built up into hæmoglobin. In the cases in the following table there has been successful treatment by iron, and the average total amount of hæmoglobin is still practically that of the uncured cases.

TABLE VI.—*Cases of Chlorosis showing Effect of Treatment.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c of oxygen per 100 grms. of body-weight.	Date.
M. W., 32 years	77·0	20·7	372	54·0	3720	3·680	51·0	7·3	0·73	
M. G., 17 years	64·0	20·6	310	65·0	2583	7·040	44·0	5·8	0·70	
M. O'H.	68·4	11·3	602	81·0	4000	5·827	54·0	7·4	1·11	
E. C., 18 years	79·5	23·2	342	40·0	4574	3·012	43·0	10·6	0·79	27.4.00
„	74·0	20·0	370	64·0	3083	4·950	44·5	6·9	0·83	12.5.00
„	65·5	14·8	442	85·0	2800	4·380	49·5	5·7	0·89	24.5.00
N. H., 17 years	69·3	21·0	330	49·0	3626	3·060	44·0	8·2	0·75	22.6.00
„	50·0	14·2	350	50·0	3723	3·500	44·0	8·4	0·79	9.7.00
„	68·4	17·5	390	85·0	2468	6·060	48·0	5·1	0·79	9.9.00
Average of final observations			—	74·0	3114	5·399	49·3	6·2	0·84	

The case which offered the most stubborn resistance to treatment by salts of iron was that of B. N., already described (Table III), in which the hæmoglobin amounted to about 70 per cent. of the normal total. The cure of such a case would involve an increase in the total amount of hæmoglobin. In typical cases, the curative effect of iron salts must be exercised otherwise than simply in the upbuilding of hæmoglobin. The essential process in the cure of chlorosis is the reduction in the volume of plasma.

Hayem ('Du Sang,' p. 708), from a study of the corpuscles during the progress of the cure, came to the conclusion that three periods in the process should be recognised. During the first stage he remarked that there is an increase in the number of corpuscles per c.mm., without any increase in the corpuscular richness in hæmoglobin. In the second stage there is a further increase in the number of corpuscles, and at the same time an increase in the amount of hæmoglobin in each corpuscle. During this period the number of corpuscles per c.mm. occasionally rises beyond the normal, and in these cases a last stage occurs in which the number of corpuscles is gradually diminished

while the enriching in hæmoglobin of those remaining continues. This apparently anomalous fact finds an explanation in the proof already given, that in chlorosis the total number of corpuscles in the blood is much increased.

Cabot, to quote another recent authority, states that, after severe anæmia, the blood on recovery may contain 7,700,000 corpuscles per c.mm. One of the cases, M. G. (Table VI), which had just recovered from a very severe condition of chlorosis, had 7,000,000 of red, and 11,000 white corpuscles. Two other cases had about 6·0 millions of red corpuscles. This phenomenon is not always to be observed, and must depend, in any case, on the extent to which the enrichment in hæmoglobin, and the reduction in the number of the corpuscles, correspond with the reduction of plasma.

The explanation which the observations in the above tables offer of the various symptoms of chlorosis need not detain us now. The disease occurs in well-nourished subjects, who gain, rather than lose, in weight during the onset. Further, the progress of the disease is not infrequently extremely rapid. Clifford Allbutt ('System of Medicine') describes a remarkable case, which occurred under his own observation, where the condition became fully established in a single night. The cure may be correspondingly rapid. Gowers ('Lancet,' 1878) describes a case in which, under treatment, the corpuscles rose from 1·29 millions to 2 millions in a week, and in twenty-six days reached 3·80 millions per c.mm. These general phenomena, in which chlorosis contrasts so markedly with the anæmia from loss of blood, find a ready explanation in the observations set forth above.

In regard to the functional changes in the body, direct investigation has not yet been undertaken; but the same data can be readily applied in the interpretation of the circulatory and respiratory changes. The fact that such a large volume of blood has to be sent through the vessels in one round of the circulation, throws greatly increased work on the heart, and diminishes the value of any given quantity of the blood for respiratory exchange. We may in this way explain the quick action, as well as the hypertrophy and dilatation, of the heart, which occur in many cases of chlorosis. Similarly, we may hope to obtain some light on the controversy as to the cause

of the functional cardiac murmurs which are so frequently present in anæmia. The suggestion arising from the results is that the increased volume of fluid leads to an abnormal tensity of the valves and vessel walls, especially during the active propulsion of the beat.

In the last place, these results offer an explanation of the dyspnœa, which is another characteristic of chlorosis. While the blood as a whole has a normal capacity for oxygen, the increase in quantity renders it unwieldy as an oxygen carrier. Further, the dyspnœa may be due in some measure to the overloading of the blood with carbonic acid. The action of aiding in the expulsion of carbonic acid from the blood in the lungs, which has been ascribed to the hæmoglobin, will be reduced; consequently the blood may leave the lungs without being sufficiently freed from the carbonic acid in the plasma.

Pernicious anæmia.

The usual age of the patient, the severity of the changes in the blood, and the ordinarily fatal issue, in spite of treatment, serve to make the clinical distinction of pernicious anæmia from chlorosis quite clear.

As regards the changes in the blood, generally speaking the morphological elements are modified much more profoundly than in chlorosis. We need not, however, concern ourselves with details on this point. In many, if not in all cases of this disease the decrease in the number of corpuscles is more marked than the decrease in the percentage of hæmoglobin. The average richness in hæmoglobin of each corpuscle is greater than in the normal corpuscle, and still more than in the corpuscle in chlorotic blood. Apparently the destruction of corpuscles goes on faster than the destruction of hæmoglobin, and each of the corpuscles remaining is enriched. Much of the hæmoglobin set free in the destruction of corpuscles is disintegrated, and is deposited in the tissues as iron-containing pigment.

There is no doubt, however, a considerable amount of indefiniteness as to the diagnostic value of the histological changes in the blood. So much is this the case that certain observers have asserted that cases of secondary anæmia occur, due to parasites in the intestine, or to cancer, which are microscopically

indistinguishable from cases of so-called typical pernicious anæmia. There is admittedly, also, a corresponding indefiniteness regarding the clinical features of the disease.

The carbonic oxide method gives us the means of furnishing, for the description of the cases, definite data regarding the volume and total amount of hæmoglobin of the blood, and in so doing explains some anomalies regarding the diagnostic value of observations on the numbers of corpuscles, etc., per c.mm.

TABLE VII.—*Cases of Pernicious Anæmia.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
A. M., 39 years	43·3	17·0	254	32·0	4305	1·100	56·2	7·6	0·4
J. C., 41 years	36·4	18·96	192	16·7	6190	0·625	58·0	10·6	0·33
J. O'H., 45 years	42·0	16·8	250	43·0	3125	1·616	62·7	4·9	0·45
A. C., 34 years	34·7	14·6	237	32·0	4017	1·156	35·0	11·4	0·67
F. Z., 32 years	32·0	21·0	152	26·0	3166	1·050	64·0	4·9	0·23
H. W., 45 years	32·7	13·0	250	23·0	5681	0·700	61·0	9·3	0·38
J. T., 60 years	33·0	23·0	141	15·0	5222	0·500	44·5	11·7	0·31
Average.....	—	—	210	26·5	4529	0·949	54·4	8·6	0·40

One point of explanation should be given here. When the hæmoglobin is reduced below 20 per cent. per c.mm., the difficulty of making exact observations increases so much that the results must be regarded as only approximately correct.

The first point which becomes clear from this table is that in the extent of the loss of hæmoglobin we have a direct measure of the gravity of the anæmia. Absolute loss of hæmoglobin, which in chlorosis practically does not occur, is seen to be here of primary importance. The severest case now recorded is that in which the total hæmoglobin had fallen to 28 per cent. of the normal. The average is 48 per cent., and contrasts with the average of chlorosis, which we found to be 95 per cent.

The loss in hæmoglobin, being a diminution of oxygen capacity, is doubtless the explanation of the occurrence of fatty

degeneration in the heart muscle and vessel walls, which is so characteristic of the disease. It is probably also the explanation of other general signs of weakness which cannot be related to definite structural changes.

While the destruction of hæmoglobin is by this method, again, shown to be a most essential part of the pathology of the disease, it is at the same time evident that the volume of the blood varies enormously. In some cases it may rise to three times the normal amount, while in others it is normal, or even subnormal. Percentage observations are therefore of little value in guiding us to a correct estimate of the condition of the blood. A given case, with 500,000 corpuscles per c.mm., may be actually much more plentifully supplied with hæmoglobin than another with double that number. The variations in volume not only explain anomalies of the kind just illustrated, but also account for a good many of the symptoms of the disease. The importance of the mere volume of the blood can best be illustrated by a short account of two of the cases which came under my observation, A. M— and J. O'H—.

When A. M— came first under observation in the hospital he was so weak that he was confined to bed. He had then a large volume of blood, about 60 per cent. beyond normal. At the same time his blood contained little over half the normal amount of hæmoglobin. Under treatment he rapidly reduced the volume of the blood to considerably below normal. The total amount of hæmoglobin increased slightly. This reduction in volume was accompanied by a striking improvement in his symptoms. He soon began to go about, and lost the nervous depression and sense of weakness which had been so marked previously. He improved also in colour, and from being somewhat pale he acquired a pronounced, if still slightly suspicious, colour.

J. O'H— was a patient of Dr. Tate, of Downpatrick. He had been under treatment for some time. Dr. Tate kindly sent him up to my laboratory in Belfast, and he accomplished the journey without undue effort or exhaustion. Yet his total amount of hæmoglobin was under 50 per cent. of the normal. He had, however, about the normal volume of blood. His history was that shortly before I saw him he had improved greatly under a course of treatment by arsenic. Before he came under Dr. Tate's care he was for five weeks unable to leave his bed.

The only difference between these two cases which was discoverable was the difference in volume. The one, A. M—, with about 50 per cent. of hæmoglobin and large volume, was unable to leave his bed. The other, J. O'H—, with practically the same amount of hæmoglobin and normal volume, was able to go about freely. A. M— improved enormously when the volume was reduced to normal, although the hæmoglobin was only slightly increased.

Some estimates of the volume of the blood in pernicious anæmia have already been published by clinical observers. Dr. Brakenridge ('Edin. Med. Journ.,' vol. xxxviii, p. 409) published a case in which the treatment was the transfusion of normal blood. From the data obtained he calculated the volume of the blood, and found it was $\frac{1}{13}$ of the body-weight, *i. e.* much larger than the normal ($\frac{1}{21}$). The calculation was made from the fact that the injection of a given amount of normal blood caused a rise in the number of the corpuscles per c.mm. It was easy to calculate from this the total volume. This method cannot be put forward as possessed of exactitude, but so far as it goes the results are in agreement with those now given by the carbon monoxide method. In one of his cases Dr. Brakenridge transfused three times, and the patient was much improved thereby. He calculated the blood on the first occasion as $\frac{1}{13}$ of the body-weight. He apparently did not calculate the volume at the second and third transfusions. If this be done, however, from the data he gives we find the volume at the second transfusion was $\frac{1}{16}$, and at the third occasion $\frac{1}{26}$ of the body-weight. The patient after the last transfusion left the hospital "cured."

Similar calculations can be made from the data published by Hayem and others.

Another interesting aspect of the question of increase in volume is the bearing which it apparently has on the prognosis in a given case. In certain cases the exhibition of arsenic has a most striking curative effect; in others it fails. In one case in the table (F. Z—) where arsenic failed to have any effect, the volume of blood was scarcely beyond the normal. The patient died shortly after the date of the examination of the blood. It therefore seems probable that an important element in prognosis is to know whether there is increased volume. Should the volume be increased, the reduction of it by curative

measures will give marked alleviation of the symptoms. This, however, is clearly only one element in the prognosis.

The following table gives a series of observations on one of the cases. The period of observation extends from January to July, and includes one of the so-called "periods of remission." The volume is rapidly reduced, with marked improvement of the symptoms at the beginning of the period. At the same time the capacity for oxygen slowly increases. During the middle period the oxygen capacity continues steadily to increase, and the volume rises again to a little above normal. After the patient left hospital the oxygen capacity and volume again fell. Later another stage is reached, when the volume rises rapidly, and the oxygen capacity continues to descend steadily. The patient left hospital a second time, and died about a fortnight later.

TABLE VIII.—*Case of Pernicious Anæmia.*

Name.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal=100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.	Date.
A. M.	43·3	17·0	254	32·0	4305	1·100	56·2	7·6	0·45	21.1.00
	50·8	18·6	278	71·0	2090	3·200	57·7	3·6	0·48	10.2.00
	51·4	15·4	333	64·0	2775	3·104	60·0	4·6	0·55	28.2.00
	51·6	11·8	437	74·0	3190	3·120	60·0	5·3	0·73	31.3.00
	Patient at this point left hospital and began light work.									
	59·2	15·4	384	77·0	2666	2·933	60·0	4·4	0·64	20.4.00
	Patient came back to hospital about May 15th.									
	52·4	15·7	333	80·0	2250	—	57·0	3·9	0·58	21.5.00
	53·5	17·4	302	40·0	4081	1·540	60·0	6·8	0·50	16.6.00
	40·7	15·5	262	31·0	4517	1·210	60·0	7·5	0·43	2.7.00
	Patient left hospital middle of July, and died August 1st.									

Anæmia from Hæmorrhage.

Another form of anæmia frequently seen in hospital is that due to hæmorrhage from a gastric ulcer. The carbonic oxide

method enables us to discover the amount of blood lost during the hæmorrhage. It is interesting to observe that the average hæmoglobin is practically the same as that of the severe cases of pernicious anæmia. In the light of this result, it is of great interest to compare the morphological changes in the blood in these cases, as well as the clinical symptoms, with those of pernicious anæmia, where the loss of blood is due to hæmolysis. I have not yet had the opportunity of examining by this method a case in which a severe hæmorrhage has given rise to pernicious anæmia. The cases in the subjoined table, with the exception of the last, were examples of hæmatemesis of the most severe form. The last case was an example of copious hæmorrhage at parturition. The patient was examined seven weeks after hæmorrhage occurred. Her tissues were overloaded with fat, and she weighed 90 kilos. The oxygen ratio of ·24 is correspondingly small. Fat subjects have, relatively to their weight, a small amount of blood. The volume of the plasma in this form of anæmia is not much increased as a rule. The case H. McG— had made substantial progress toward recovery. Her blood was, when examined, in the condition characteristic of chlorosis. The hæmoglobin percentage was below fifty, while the red corpuscles were in normal numbers.

TABLE IX.—*Cases of Anæmia from Hæmorrhage.*

Name and age.	Vol. of dry CO absorbed in c.c. at 0° and 760 mm.	Percentage saturation of hæmoglobin with CO.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin. Normal = 100.	Total volume of blood in c.c.	Red corpuscles in millions per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. of body-weight.	C.c. of oxygen per 100 grms. of body-weight.
N. M., 24 years	69·6	33·7	206	38·0	2901	2·690	55·0	5·2	0·37
S. M., 21 years	47·7	24·7	193	35·0	2969	—	49·0	6·6	0·39
H. McG.	46·5	16·2	287	42·0	3679	4·845	55·0	6·6	0·52
M. M., 21 years	50·0	21·2	235	38·0	3310	3·656	52·0	6·3	0·45
S. M.	33·0	17·7	186	23·0	4325	1·056	50·0	8·6	0·37
M. B., 39 years	47·2	21·8	216	21·0	5450	3·092	90·0	6·0	0·24
Average.....	—	—	220	33·0	3926	3·067	58·0	6·5	0·39

Summary of Conclusions.

1. The anæmia of chlorosis is due to an increase in the plasma of the blood, the total hæmoglobin remaining normal in amount.
2. In pernicious anæmia the total amount of hæmoglobin becomes reduced in proportion to the severity of the disease. The volume of plasma may be increased or reduced.
3. In the anæmia after hæmorrhage the volume of plasma is not much increased.
4. There is no evidence that salts of iron aid in the cure of anæmia by the direct upbuilding of hæmoglobin.

I have to express my hearty thanks to my colleagues on the Staff of the Royal Victoria Hospital, and to many other friends in the medical profession in Belfast, for affording me such ample facilities for carrying out this investigation. I am indebted to Dr. Thomas Houston for assistance in making the observations.

WILLIAM HUNTER

referred to the importance—in studying the blood both in health and disease—of appreciating the close relationship between the various parts of the blood—plasma, red corpuscles, and leucocytes; the last, in respect of complexity of composition, functional activity, and power of influencing the constitution of the blood, being really the most important of the three parts.

His contribution to the discussion would relate more especially to the features characterising hæmolytic anæmia.

As regards the factors concerned in disease of the blood, there were three great groups: 1, one special to the blood, viz. actual loss by mechanical injury (*traumatic*); 2, *nutritional* or *assimilative*; 3, *infective*.

The changes, quantitative and qualitative, produced by defective nutrition or assimilation, interesting though they were, were in his opinion of much less importance and significance than those produced by infective influences. They were for the most part quantitative rather than qualitative; and even quantitatively it was remarkable how little change in the blood was

produced by even the severest assimilative disturbances. The whole group of "secondary" anæmia illustrated this.

On the other hand, the changes induced by infective influences were of a profounder character, even although their effects were often hardly demonstrable—being qualitative rather than quantitative.

These qualitative changes might affect all parts of the blood: both the *structural* part—the nucleo-proteid (stroma)—of plasma, red corpuscles, or leucocytes; and the *formed* part—*e. g.* the hæmoglobin of the red corpuscle or the albumin of the plasma.

Thus in the case of the plasma, the varying size, consistence, and other peculiarities of clot, so often noted and described by old observers in times of venesection, were doubtless manifestations of changes in quality of the nucleo-proteid (fibrinogen) produced by disease.

The liability to hæmorrhage, so often noticed in septic disease, was similar evidence of qualitative change; as also the converse condition, increased coagulability (*e. g.* peripheral thrombosis), in the same class of case. But the most striking evidence of qualitative change was afforded by the phenomena of immunity, and the other various properties—bactericidal, globulicidal, agglutinating, hæmolytic, etc.—conferred on blood by the influence of infection; properties doubtless springing from the leucocytes in the first instance, but transferred to the constituents of the plasma, since these properties were still retained even by the serum.

How profound was this change was shown best by two facts: the remarkable rapidity with which it was effected, and (in the case of certain diseases) its no less remarkable permanency. The change was probably one affecting the nucleo-proteid constituent (constituting the *stroma* of the blood).

The effect of infective disease was not confined, however, to mere changes in quality. In some cases no less remarkable were the changes in quantity. And when the two were combined together, we had a degree of blood-change surpassing anything met with as the result of ordinary infective disease on the one hand, or ordinary malnutrition on the other.

This change was specially striking when the action of the infective agent or poison on the blood was not merely qualitative but actually destructive—hæmolytic.

The result was then a change in the blood possessing certain more or less distinctive characters, constituting what he might describe as those of *hæmolytic anæmia.*

Such a type of blood disease was, according to his studies, most typically exemplified by the condition—pernicious anæmia, still regarded by many as merely an extreme condition of ordinary anæmia, the final stage of many blood conditions; but really constituting, according to him, not merely a special variety of anæmia, but a special disease of definite infective nature, localised to the alimentary tract.

The features of a hæmolytic anæmia in its most pronounced form he found to be—

1. *Oligocythæmia* far more rapid in production and profounder in degree than that met with in any other form of anæmia, and often producible with hardly any noticeable change in the blood apart from the actual reduction in the corpuscles.

This was very notable in pernicious anæmia, where one often met with a reduction to 15 or 20 per cent. of the normal number, without apparently the slightest cause.

Whereas as the result of copious and repeated bleedings, lasting weeks or months, one might still find the reduction only to 30 or 40 per cent.

This feature of rapidity of production, and great degree, was equally brought out by his experiments. Thus—

(1) In one case, a fall from 5,350,000 to 4,240,000 per c.mm. in 24 hours was produced by half a gramme of pyrogallic acid, without the slightest appreciable disturbance in the animal's health, or the presence of any morphological changes in the general circulation.

(2) In another, a fall from 5,890,000 to 4,650,000 in 5½ hours; to 1,100,000 the following day; and to 550,000 on the day after —produced by 1½ grammes of pyrogallic acid.

Compared with effect of bleeding this change was very marked.

Thus (Exp. 79) a fall from 4,560,000 (91 per cent.) to 2,640,000 (52 per cent.) in 24 hours, with rapid recovery to 3,750,000 (75 per cent.) in 4 days, as the result of withdrawing about 35 per cent. of the total blood.

A fall from 3,750,000 (75 per cent.) to only 3,490,000 (69 per cent.) in the same animal in 24 hours, as the result of with-

drawal of further 20 per cent. of total blood. Recovery to 5,000,000 (100 per cent.) in 14 days.

Exp. 80: a fall from 4,500,000 (90 per cent.) to 3,010,000 (60 per cent.) in 24 hours as the result of withdrawing 36 per cent. (40 c.c.) of total weight. Recovery to 4,860,000 (97 per cent.) in 9 days.

The withdrawal of further 70 c.c. (63 per cent.) with fall to 2,960,000 (59 per cent.) in 24 hours, and 63 per cent. on following day. Recovery to 4,600,000 (92 per cent.) in 12 days.

2. *Variations in form and size of red corpuscles* greater than ever observed in ordinary anæmia, and specially striking (as the lantern slides show) when hæmolysis is in active progress; changes in the red corpuscles in the circulating blood being then seen, which were never observable under any other conditions, and usually only observed in the blood of the spleen, the chief seat of hæmolysis according to his observations.

3. *High ratio of hæmoglobin.*—A striking feature of the blood, denoting plenty of iron in the body available for blood formation; more than normal.

The following are some figures noted in certain of his recent cases of pernicious anæmia:

Corpuscles	. .	36 per cent.	...	Hæmoglobin	. .	38 per cent.	
„	. .	37 „	...	„	. .	54	„
„	. .	25 „	...	„	. .	40	„
„	. .	24 „	...	„	. .	40	„
„	. .	27 „	...	„	. .	34	„
„	. .	32 „	...	„	. .	40	„
„	. .	18 „	...	„	. .	22	„
„	. .	21 „	...	„	. .	40	„

The disparity betwixt percentage of corpuscles and hæmoglobin usually became less marked when the values were very low, or when hæmolysis was very active, but it always reappeared again when the stage of acute destruction was past.

This high ratio of hæmoglobin was to his mind a very notable feature, both pathologically, and from the diagnostic point of view. When present, it alone served to distinguish that anæmia as hæmolytic in origin, and not the result of loss of blood.

In the latter the positions were invariably reversed—the hæmoglobin percentage was lower than the corpuscular one.

4. *Change in quality of hæmoglobin.*—With the foregoing were usually associated other changes, viz. a relatively loose association and irregular distribution of the hæmoglobin with the stroma; and a change in quality of the hæmoglobin itself—one evidence of which is an altogether unusual facility for crystallisation, as shown by Dr. Copeman.

5. *Nucleated red corpuscles.*—Occasional presence; but in his experience by no means so common as described by others. Irregular distribution of the hæmoglobin within the altered and deformed corpuscles, often simulates in appearance nucleated red corpuscles. The only way in his experience to judge of the presence or absence of nucleated red corpuscles was by staining dried specimens, the nucleus in the real corpuscles then staining blue, while in the simulated red corpuscle the whole body remained stained with eosine.

6. *Leucocytosis* often accompanied a certain degree of hæmolytic anæmia; and in some diseases—the inflammatory—was probably in part the cause of the hæmolysis. But that it was not a necessary feature was in no way better evidenced than by the fact, that in pernicious anæmia it was the exception to find any change in the number of leucocytes.

Related to these hæmolytic changes in the blood were certain definite clinical features during life, and certain pathological changes after death. Among the former were:

7. *Polycholia* or *polychromia,* a very large increase in the pigments of the bile, a degree of richness in bile pigments, in his pathological experience exceeding anything ever met with in any other disease.

It was a feature so marked that it was one he sought for *post-mortem,* as one of the constant changes in the disease; and with this, and doubtless related to it, was a corresponding increase of pigments and chromogens in the urine; chiefly urobilin.

8. *Urobilinuria,* which came and went, and in degree afforded a perfectly reliable index of the degree of blood destruction.

That the urobilinuria in such cases depended in some degree upon a certain *kind* of blood destruction, and a certain abnormal kind of urobilin, his observations had satisfied him.

When the destruction was so rapid as to cause hæmoglobinuria, urobilin was increased slightly before the attack, and

very largely (5 to 10 times) after the attack; but was only present in moderate quantity during the attack, as some observations he had made in a recent case had shown.

Relation of Urobilinuria and Hæmoglobinuria.

A man aged 25. Seen February 24th, 1898.—Red corpuscles 1,113,000 = (22 per cent.); hæmoglobin 22 per cent. Illness began four years ago with an attack of paroxysmal hæmoglobinuria after a bicycle accident. Attacks since then from time to time. Average, one every six months, usually brought on by cold preceded by shivering, lasting thirty-six to forty-eight hours. Last attack three weeks ago.

March 11th, 1898.—Urine dark, deposit of urates; sp. gr. 1025; no albumin; urobilin in considerable quantity.

March 12th, 1898.—Another specimen 1025, very dark, heavy deposit of hæmoglobin *débris*; no red corpuscles; a few pigmented renal cells; heavy deposit of albumin; *urobilin* moderate quantity.

March 16th, 1898.—Urine 1015, better colour, no deposit, no albumin; urobilin in very large quantity, estimated to be 5 to 10 times more.

9. *Hæmoglobinuria* was an uncommon feature of active hæmolysis, and depended, as he had shown, on the seat and nature of the destruction rather than on its amount. The slightest amount of hæmoglobin set free within the general circulation at once appeared in the urine; whereas a most extensive destruction could occur within the portal area, notably the spleen, without any hæmoglobinuria occurring.

10. *Jaundice.*—The jaundice associated in small or great degree with increased destruction, was, according to his studies, related, not to the amount of hæmoglobin set free, or the amount of bile-pigments formed from it, but to the nature of the poison causing the destruction.

In all cases the jaundice was obstructive, but the obstruction was intra-hepatic—the result of intra-hepatic catarrh, produced by the irritant action of the poison (or other products of destruction) on the bile-passages in course of excretion.

11. *Pigment changes in organs.*—The last change he had to note as a consequence of increased blood destruction was pigment changes in certain organs. These were found chiefly in the liver and kidney, and under certain conditions also in the spleen.

The excess in pernicious anæmia was very notable, as he had formerly shown, and as all his subsequent observations fully confirmed. It served with absolute certainty, in his judgment, to distinguish pernicious anæmia from the two conditions which *clinically* often seemed to resemble it, viz. the anæmia of cancer of the stomach, and of loss of blood.

Analyses on the last three cases of pernicious anæmia he had observed, gave a percentage of iron in milligrammes of—

Liver, 360; *Spleen*, 63; *Kidney*, 48;

while analysis in a case of cancer of the stomach, which presented the typical lemon appearance so often associated with pernicious anæmia, gave a percentage of iron in milligrammes of—

Liver, 22; *Spleen*, 13; *Kidney*, 3.

In other words the amount of iron in pernicious anæmia was, for the *liver*, 16 times; *spleen*, 5 times; and *kidney*, 16 times greater than in the disease which it is generally said to resemble most closely.

The character, amount, and distribution of this pigment, also presented certain important features, which he demonstrated by lantern slides thrown on the screen.

ARTHUR WHITFIELD

said that he had worked at the morphological side of the blood only, and would therefore confine his remarks to that subject. In this connection he thought that the work of Ehrlich had, perhaps, not received such full recognition as it deserved. Several amended views had appeared in correction of Ehrlich's original statements, and some of these he ventured to think were incorrect. Among these he might instance the change of nomenclature from "neutrophile" to weakly "acidophile" as applied to the granules in the polymorphonuclear leucocyte.

He had noticed that when a mixed methylene blue and eosin solution was used these granules stained fairly well, but when an eosin solution was used followed by methylene blue or log-wood the results were somewhat different. If the films were stained by a 2 per cent. watery solution of eosin and then examined wet, it would be found that the whole so-called neutrophile cell had taken on a diffuse pink stain and the granules, though visible, were not selectively stained. If now the specimen were after-stained with methylene blue, in some instances the granules showed up fairly well; but the method was uncertain, as the after-staining generally resulted in a preponderance of either methylene blue or eosin. If, on the other hand, the films were stained first with the usual ½ per cent. eosin solution in 70 per cent. alcohol, and after-stained with methylene blue or hæmatoxylin, no granules were shown at all when the specimen was mounted in balsam. Phear had pointed out that by his method, when using a solution of eosin in 40 per cent. alcohol, the so-called "fine oxyphile granules" of the polymorphonuclear cells were not at all deeply stained. It was very important to refer to balsam specimens only in stating whether the granules were stained or not; as they were easily seen in water specimens, it was extremely difficult to be certain whether the granules were selectively stained or not, unless the staining were quite strong. In balsam specimens, on the other hand, the granules were not seen at all unless stained.

A good deal of work had been done on the changes in the blood in diseases of the skin, etc.; and, as is not uncommonly the case, diagnostic importance had been laid on certain changes noted which had afterwards been found to be common to many disorders. The first point had been the discovery of eosinophilia, in the blood of patients suffering with pemphigus, by Gollasch and Neusser. Not very long afterwards Leredde had discovered the same change in the blood of patients suffering from dermatitis herpetiformis, and also in the serum drawn from the bullæ in these cases. Leredde had insisted that the discovery of eosinophilia in the blood and blister serum in any bullous disease was sufficient to make the diagnosis of dermatitis herpetiformis. This conclusion had been hotly contested by almost all other workers, and if Leredde still held to his

opinion he was probably the only one who did so. Vysin had worked through a rather long list of diseases of the skin with the intention of determining the characteristic changes present, if any; and he (Dr. Whitfield) had done the same, though he had not hitherto published his results as they agreed entirely with those of Vysin and did not lead to any definite conclusions. The diseases which the speaker had investigated included cases of psoriasis, eczema, erythema induratum, pityriasis rubra (Hebra's type), acquired ichthyosis, generalised lichen planus, pemphigus, dermatitis herpetiformis, and hydroa gestationis, syphilis and mycosis fungoides. Of these eczema, psoriasis, lichen planus, pityriasis rubra, and acquired ichthyosis had much in common and might be taken together. There was a tendency to polynuclear leucocytosis present in most of them and this seemed to depend far more on the extent of the eruption than upon its nature. In two cases, namely, widespread chronic psoriasis and pityriasis rubra (it is worthy of remark that in the latter with a universal eruption leucocytosis was not present), there were present simply nucleated cells with well-marked neutrophile granulation. These cells would, of course, be reckoned as Ehrlich's myelocytes, but they were of the usual size of the ordinary hyaline cell. Vysin had found large numbers of these cells present in some cases of chronic wide-spread eruptions, but in the two cases quoted they were present in a proportion of under 1 per cent. The pemphigus cases and dermatitis herpetiformis all showed well-marked eosinophilia, both in the blood and in the blister fluid, the numbers varying from 8 per cent. to 25 per cent. in the blood, and from 61 per cent. to 96 per cent. in the blister fluid. Eosinophilia was noticed occasionally in some of the other wide-spread chronic eruptions, but to nothing like the same extent. The case of mycosis fungoides was of some interest, since the blood-count coincided almost exactly with that found in four cases of lymphoma of the chest and neck, respectively. In both of these cases the tendency of the blood was to become mononuclear, and especially the large hyaline cells were increased. The interest lay in the fact that the histological findings in the skin of this disease were such, that many considered it to be a lymphomatous condition of the skin.

In conclusion, he would like to draw attention to the work of

Justus on the blood in syphilis. Justus had stated that in any stage of constitutional syphilis the patient's blood would show, on inunction with mercury, a rapid diminution of the hæmoglobin within the first few days, followed by a slowly continuous rise up to the normal as the disease itself became influenced by the mercury and the patient improved. This change was not noticed when healthy people were rubbed with mercury, and could therefore be used as a point in the diagnosis of the disease. It appeared that this might be of great value, as it had been corroborated by many observers, and the speaker could only say that he had found it perfectly true.

A DISCUSSION ON THE PATHOLOGICAL UNITY OF TABES AND GENERAL PARALYSIS.

F. W. MOTT, F.R.S.

(*November 21st, December 5th, December 19th,* 1899.)

SYPHILIS is the best example of a poison probably, though not proved to be, of microbial origin, which has a selective influence upon the nervous system with a remote effect. It is, in my opinion, the most important factor in the production of two progressive degenerations of the nervous system, one affecting especially the exogenous afferent spinal neurones, namely, locomotor ataxy, the other affecting the association system of neurones of the cerebral hemispheres, especially of the frontal and central convolutions, namely, general paralysis of the insane. A striking instance of the selective action of the syphilitic poison is shown in the fact that only in persons affected with acquired or inherited syphilis is the symptom known as the Argyll-Robertson pupil found; indeed, it is sometimes the only symptom. Seeing that this is the most common objective phenomenon in the two diseases mentioned, it strengthens the presumption, based on experience, that the syphilitic poison is the cause of the disease in the majority of instances. It is the opinion of many authorities—and I must say that my experience supports it—that locomotor ataxy and general paralysis are one and the same morbid process, affecting different parts of the nervous system. They are both, in my opinion, a primary and progressive decay of the nervous elements, and are ætiologically, clinically, and pathologically very closely related. Baillarger, in 1862, recognised clinically the tabetic form of general paralysis, and later, in 1862, Westphal demonstrated the anatomical lesion in the posterior columns of the cord. Since then a discussion has occurred in which a number of neurologists and alienists have taken part as to whether tabes and general paralysis can be looked upon as the same morbid process affecting different parts of the nervous system. It is acknowledged by all authorities: (1) That a certain number of cases of tabes present mental symptoms; (2) That a certain number of cases of general

paralysis present tabetic symptoms, and that after death atrophy, and sclerosis of the posterior columns are frequently found; (3) That a certain number of cases of tabes develop subsequently mental symptoms, and die of general paralysis. Examples of all these conditions have come under my notice. Syphilis was recognised by a great number of authorities as the most important ætiological factor of tabes; but only more recently has the doctrine of Fournier been widely accepted for general paralysis. Lastly, a number of authorities have examined the spinal cords and roots from cases of the tabetic form of general paralysis. One set of observers—Raymond, Rendu, Flechsig, Nageotte—claim that the lesion is of the same nature as tabes, while Ballet, Joffroy, Geil, Hoche, hold the opposite opinion. The fact that there is generally lateral column degeneration associated with the posterior column sclerosis is no argument against the unity of the processes, for in nearly all cases in which there have been convulsive seizures it has been found that there is pyramidal degeneration, and this has been accounted for by the death of the pyramidal neurones of the Rolandic area.

Marie and other authors contend that the degeneration of the posterior columns in general paralysis is endogenous, and not exogenous. He maintains that in general paralysis, in contradistinction to tabes, the cornu radicular zone remains intact, whilst, on the other hand, there is disease of the endogenous fibres corresponding to the comma tract. This very probably is true if a selection of cases be not made. Luderitz examined sixteen cases of general paralysis, and found that the degeneration which occurred in the posterior columns did not coincide with that found in tabes. It is, however, necessary to select cases which presented symptoms of tabes during life, but care must be taken to avoid the fallacy of selecting cases of tabes with mental symptoms, but not the symptoms characteristic of general paralysis. The close association of tabes and general paralysis is to my mind clearly shown by the fact that there are a considerable number of cases in which it is difficult to say whether they should be classed from their clinical symptoms and the morbid changes found after death, as tabes with mental symptoms, or as cases of tabetic general paralysis. I have seen cases in which the diagnosis of general paralysis has been made because the patients were suffering with mental

symptoms indicating that disease, viz. maniacal or melancholic symptoms and delusions associated with ataxy. After a time the mental symptoms have cleared up, and the case has then been called tabes. Again, I have frequently seen cases of tabes which begin with all the characteristic phenomena of this disease, and then terminate in progressive dementia and paresis, dying in an asylum from general paralysis. Symptoms which are looked upon as characteristic of tabes, such as grey atrophy of the discs, are not uncommon in general paralysis (6—7 per cent.),[1] and I have met with symmetrical perforating ulcers and Charcot's disease of joints.

I have recently examined twelve cases of the tabetic form of general paralysis in which the changes in the brain (naked-eye and microscopical) were characteristic of general paralysis, and the cords showed the characteristic lesions of tabes, viz. atrophy of the exogenous systems of fibres, the endogenous being spared. I throw on the screen photomicrographs illustrating these facts, as well as a table showing the principal clinical and pathological phenomena of these cases. My experience would point to about 5 per cent. of the cases of general paralysis being associated with true tabetic cord lesions. The ætiological relationship of the two diseases is almost identical; both affections occur usually in the prime of life, are more prevalent among townspeople, affecting men of all grades of society; but as a rule only women of the lower and lower middle classes. Again, juvenile general paralysis and juvenile tabes probably occur only in the subjects of congenital syphilis, and the sexes are here affected with equal frequency. I have met with one case of the latter and twenty-five cases of the former, with twenty *post-mortem* examinations. In 80 per cent. of juvenile paralytics a definite history of syphilis or signs of it were obtained. In the majority of adult cases of general paralysis and tabes a history of syphilis is forthcoming. In a certain number of cases, it is true, no such history can be examined, but it may be pointed out that Dr. Crocker was unable to obtain a history of syphilitic infection in 20 per cent. of cases of indubitable syphilitic skin affections.

[1] From an examination of the whole of the cases of general paralysis dying in Claybury Asylum during the last two years, 130 in number, I find that the notes record primary atrophy of the optic nerves (visible to the naked eye) in nine, *i. e.* 6 to 7 per cent. If the cases of juvenile and tabetic general paralysis are included, the percentage would reach 10 per cent.

Syphilitic signs on the body are much more frequently met with in general paralysis than in other forms of insanity. Persons inhabiting countries where syphilis is uncommon are very free from general paralysis and tabes. A considerable number of cases are now on record of married couples being affected with general paralysis. I have recently seen a man with well-marked signs of syphilis, who subsequently died from the tabetic form of general paralysis; his wife, who had healthy children by her first husband, and none by this, her second husband, is now in the second stage of general paralysis.

There are two types among the juvenile general paralytics: (1) in which the syphilitic poison seemed to have produced an arrest or impaired development of the higher centres, so that the child was weak-minded or imbecile; (2) in which the child was mentally capable, in some cases highly intelligent and active-minded. The cause of the degenerative process in most of the cases seemed to be associated with the increased psychical activity which must of necessity develop after puberty, when new emotions, objects, and ambitions are awakened by the sexual instinct and the struggle for existence. That psychical activity plays a very important part in this disease as affecting adults is clearly shown by the following facts:—The sufferers are nearly all townspeople with a quick reaction time, ambitious and energetic, and the first symptom of the disease may be undue mental activity, approaching now and then to that of genius. It might be argued that a large number of these people are from the lowest and least educated classes; still, I am convinced that they belong to the mentally active class. Not only do we find the people affected possess mental activity, but also usually sexual proclivity, and it is very difficult to decide whether the increased sexual activity so frequently met with in the early stages of the disease is a cause or an effect. But all forms of mental excitement are associated with fatigue, and too often the neurasthenic condition which precedes the more definite symptoms of the organic brain affection leads to alcoholic excesses, and it is often very difficult to decide whether a case is one of *mania a potu* or of general paralysis. The two are frequently combined, and if so the disease runs a more rapid course. The researches of Bonhofer and Trömner have shown that acute degenerative changes may occur in the cortical cells as a result

of acute alcoholism; and I have found, and can therefore agree with Jolly, that in cases of alcoholic dementia there exist organic changes affecting the superficial layers of the cortex, and causing atrophy of the tangential fibres. It is, then, probable that although alcohol will not of itself produce general paralysis, it will materially accelerate the progress of the disease. Krafft-Ebing has related that nine general paralytics were inoculated with syphilitic virus, and watched 180 days without showing any signs of infection, clearly proving that they possessed immunity, and probably therefore had previously suffered with the disease. He sums up the ætiology of this disease in two words, "civilisation" and "syphilisation," and he brings forward very convincing facts and arguments in favour of the important *rôle* of syphilis. It has been argued that in Mohammedan countries, where syphilis is rife, general paralysis is unknown. The recent report for the year 1899, by Dr. J. Warnock, from the Egyptian Hospital for the Insane, entirely upsets this argument. He states:—"During 1899 fifty-seven general paralytics were under care out of a population of 500. The large towns furnished nearly all the cases of this disease, and syphilis was known to be the cause in twenty-nine of the thirty-five cases admitted. Twenty-four of them were native Egyptians."

General paralysis and primary degeneration.

The morbid process in general paralysis has been considered by Mendel and many other authorities to be a primary meningo-encephalitis. I would advance the following reasons for considering it, like tabes, a primary degeneration of the neurone with meningo-encephalitis that is secondary:—(1) Its relation to tabes dorsalis, and the probability of its being the same morbid process due to the same cause (syphilis) commencing in a different part of the nervous system. (2) The existence of the Argyll-Robertson pupil in the majority of cases. (3) The existence of grey atrophy of the discs in a number of cases too great to be accounted for by mere coincidence. The last two symptoms cannot be explained except by a primary atrophy. (4) The evidence of a wasting of the whole nervous system, but out of all proportion to the evidences of inflammation affecting some parts more than others. This wasting must be primary in the nervous system and not secondary to bodily disease, for in

no cachectic disease, or even in starvation, do we find extensive wasting take place. (5) The thickening of the pia arachnoid membrane is proportional to, and corresponds with, the degree and locality of the atrophy; so it is with tabes. (6) In many cases of tabes, especially those with mental symptoms, atrophy of the tangential and superradial association fibres of the brain are found quite similar to, but often in different situations from general paralysis. (7) In diseases with well-marked meningo-encephalitis, about which there can be no dispute that it is primarily an inflammatory process, we do not find this extreme atrophy. In illustration of this, I would call attention to three cases of African lethargy which I had the opportunity of examining, and which are described in the present volume (pp. 105, 122). In tabes we have an example of degeneration of the afferent projection system, which, for reasons already mentioned, is probably due to nutritional failure on the part of the posterior spinal neurone, by which parts most remote from the centre of nutrition undergo a regressive atrophy. The cells of origin seldom undergo marked changes unless pigmentation can be considered evidence of degeneration, but there seems to be some reason why the cells of the posterior spinal ganglia should be able to maintain atrophic independence. Possibly it is the existence of the capsule, possibly the cells receive stimuli from the viscera by sympathetic branches, or it may be that they have become more or less independent of the influence of stimuli, in consequence of the impulses from the periphery travelling directly across the T-shaped process. Again, after experimental section of the posterior spinal roots in monkeys, I did not find any change in the posterior spinal ganglion cells, after intervals of from three weeks to six months. We know, moreover, that in amputation cases of long standing, although the nerves and posterior roots waste, the spinal ganglion cells suffer little change. It is particularly the central projection of the neurone that undergoes the degenerative process in tabes, and judging from the experimental evidence above adduced, this would not suffice to cause changes in the cell. The peripheral portion of the neurone—viz. the sensory peripheral nerves—have been shown to undergo regressive atrophy and degeneration from the termination towards the centre. We know that the peripheral portion of the T-shaped

process is ensheathed by the hollow mesoblastic cells forming the sheath of Schwann, and which, there are many reasons to think, exercises an indirect trophic influence upon the long axis-cylinder process. Again, in tabes the idea that a sclerosis of the posterior columns produced by an irritative proliferation of the glia tissue is the initial morbid process, causing a secondary degenerative atrophy, involves a confusion of cause and effect. The overgrowth of the glia tissue is the result of, and proportional to, the primary progressive atrophy of the nervous elements, for we cannot suppose that the glia tissue would electively destroy exogenous fibres, leaving the endogenous intact. In support of this statement I show a photomicrograph of the sixth cervical segment of the spinal cord of a monkey, in which the third, fourth, fifth, sixth, and seventh cervical, and first, second, and third dorsal posterior spinal roots were cut on the left side. The eighth cervical, which especially supplies the hand, was not divided. This monkey was kept alive for six months, and it was after a time very difficult to determine upon which side the operation had been performed, as each hand was used equally well, the animal thus behaving quite differently from those in which all the roots had been cut (Mott and Sherrington, 'Proceedings of the Royal Society,' 1895). The result of this operation is shown in the two bands of sclerosis in the posterior column on the side of the divided roots, with an area of normal fibres corresponding to the undivided root lying between. It is to be observed in a photomicrograph of the sixth cervical segment, that fine fibres pass across the area of sclerosis to the grey matter of the posterior horn; in not a single section of all the segments of the upper part of the cord were such fibres (which could be only the terminal branches of the undivided eighth root) absent. This points to the probability of the overlapping of roots of spinal segments. It certainly shows that sclerosis does not cause atrophy of fibres, for here is a band of fibres lying between two definite bands of sclerosis with delicate fibres passing across the sclerosed area. Obersteiner has maintained that the degeneration of the posterior columns is due to a meningitis affecting the roots at their entry, thereby compressing the accompanying nutrient vessels; but against this theory there are many facts which will occur upon consideration, and I need not at present mention them.

ALEXANDER BRUCE.

I have listened with the greatest of interest to the valuable paper of Dr. Mott, and I need not in this Society say how much we all appreciate Dr. Mott's valuable contributions to neurology. With regard to the clinical aspect of this important question I do not propose to speak, because the opportunities of considering the question that have come before me have been insufficient to enable me to form an absolutely definite opinion with regard to it. But I might be permitted to refer rather to the anatomical evidence with reference to the ætiology of ataxia, and to the identity of ataxia with general paralysis. I suppose that practically every one admits now that the lesions in the cord in ataxia cannot be attributed to a primary sclerosis of the neuroglia; that the change, so far as it is intra-spinal, begins in the intra-spinal continuations of the posterior nerve-roots. It is undoubted, I think, that in every class of ataxia the fibres which are first affected are the exogenous fibres. Dr. Mott's specimens and his lantern-slide photographs showed beyond a doubt, what is now practically universally recognised, that the fibres which are spared are the endogenous ones—the fibres which form the main portion of the cornu-commissural tract, and the tract which bounds the posterior median septum, variously known as the "oval tract of Flechsig," or the "dorso-median tract" of Obersteiner, or as the "septo-marginal tract" of Bruce and Muir. Therefore we have to address ourselves to the question as to what is the cause of this degeneration of the exogenous fibres. For a long time I must confess to having been very much fascinated by the view enunciated if not first by Marie, at least first brought into prominence by him, that the change depended upon nutritive alteration in the posterior root-ganglia; that, in consequence of this nutritive alteration, the collaterals of the posterior roots within the cord, the collaterals going to the column of Clarke, to the anterior cornua, to the posterior cornu, and to the column of Gall, degenerated. This seemed an extremely simple and suggestive mode of explaining the lesion; but when one comes to consider the question further, it is difficult to see why this change should have been

so remarkably confined to the intra-spinal course of the fibres, and why it should have spared the peripheral nerves. Of course, we are well aware that in a great proportion of cases the peripheral nerves suffer also. That, I think, was first pointed out, or was very strongly emphasised, by Déjérine. But the change in the peripheral nerves is not at all proportionate to the change in the posterior roots within the cord; and it is, to me at all events, difficult to understand how a change in the posterior root-ganglion could so completely destroy the intra-spinal course of the fibres, leaving, in the first instance, undegenerated the portion of the posterior root which lies between the posterior root-ganglion and the membranes, and also leaving the peripheral nerve largely intact. I have not had much opportunity of inquiring into this point myself, but there seems to be a large body of evidence that the degeneration of the posterior root-ganglia is not proportionate to the degeneration of the fibres within the cord.

It was also stated that the collaterals were the first to suffer, and that they suffered because they had less resistive power. That is, of course, simply begging the question; it is not an explanation at all. What seems to me to be the most probable explanation—one which I observe Dr. Mott has not referred to, except indirectly—is that a pressure may be exerted on some part of the posterior root in such a way as to cut it off from its nutritive centre. Dr. Mott has referred to Sherrington's section of the posterior roots, in which he says that division of the posterior roots leaves intact the ganglia, and produces an ascending degeneration in the cord exactly analogous to the degeneration in ataxia. Therefore it seems to me that the view that deserves a great deal more consideration than it is obtaining at present is the view of Redlich and Obersteiner. This view is, that the posterior roots when they enter the cord do so in a manner altogether different from the anterior roots; that as they enter the pia mater the roots undergo a sharp constriction, and that at the point of entry the medullary sheath becomes remarkably thin, if not in parts almost entirely lost. Now the contention of Redlich and Obersteiner is that the disease begins at this point of constriction. In the early stages of ataxia, I think it is generally admitted that the degeneration begins intra-spinally; the fibres going to the posterior cornu,

the fibres going to the anterior cornu, and to the columns of Clarke, degenerate; but the posterior root between the cord and the ganglia remains intact. That is so, I think, in the first instance. Now we have at this point of entry a condition which is very much analogous to the constriction in the optic nerve as it passes through the sclerotic. We have further in ataxia the conditions which may produce an increase of constriction, and therefore a possibility of cutting through the medullary sheath and even the axis-cylinders at that point. This change is the result of meningeal thickening, œdema and vascular dilatation. At the point where the root enters there is usually, often surrounded by a nerve, a distinct blood-vessel. We see that in ataxia, even in the majority of early cases, there is a distinct thickening of the meninges at the posterior surface of the cord; and there is invariably also a considerable dilatation of the blood-vessels, which at this point are largely venous.

Now it seems to me conceivable, indeed extremely probable, that in this primary development of a meningeal thickening (whether we call it inflammatory, or subinflammatory, or simply proliferation as the result of syphilis, like that found in other organs), and in the vascular dilatation, we have the means of the constriction of the posterior root and of the possible action of the syphilitic toxin, whatever that may be, upon the remaining axis-cylinders. In that case we can perfectly well understand why the intra-spinal degeneration should be so markedly primary, and why the posterior root, between the cord and the posterior root-ganglion, should be in the first instance normal.

I have always felt that we too readily assume that the meningeal thickening is secondary to the nervous degeneration, and that it is the result of the irritation of the degenerative products of the nerve-fibres. If it were so, why do we not find always that there are thickened membranes over the degenerating direct cerebellar tract in every case of ascending degeneration? Why do we not find that there are always thickened membranes over patches of multiple sclerosis? Further, why do we find in locomotor ataxy that the degeneration or the thickening of the membranes is not limited to the part specially affected—the lumbo-sacral region—but may extend up the whole length of the cord? Are we to assume that the products of these nerve

degenerations, which are exceedingly slow in their formation, are yet so poisonous that they irritate the whole of the membranes along the dorsal and cervical regions of the cord, as well as in the lumbar centres? It seems to me we are too apt to assume that the degeneration of the neuron is the primary factor, and that the change in the vessels and in the connective tissue is secondary.

In the same way it seems to me that in the cerebral lesions of general paralysis the first changes are not specially the nervous, but the vascular and connective tissue; or, at all events, that these latter are so early that they may be regarded as concomitant results of the action of the same toxine which led to paralysis of the nerve-fibres, and not the result of the irritation or destruction of the nerve-cells or fibres.

I speak in this matter with diffidence. I should be very unwilling to put my opinion against that of Dr. Mott, because his experience is so much greater than can be that of one who has comparatively little opportunity of working with material derived from asylums; but from a number of cases which I have observed lately with my friend Dr. Ford Robertson, of the Scotch Asylums Laboratory, it seems to me—and I believe it is his opinion also, as it is the opinion of Dr. Bevan Lewis—that one of the earliest changes occurring in the cortex in general paralysis is the vascular lesion. When sections are stained by Bevan Lewis's method, whereas there is practically no staining of the vessels in the healthy cortex, there is an appearance of hyaline degeneration of arterioles in the superficial layers and of granular degeneration in the deeper layers, with distinct signs of periarteritis. This condition may be present before there is any very marked nervous degeneration. I think we are bound to entertain the idea that the change in the nervous elements is not the primary one; we are bound to consider that the change may be just as much primary in the vascular and the connective-tissue elements as in the nervous. We see, as general paralysis progresses, that very frequently inflammatory foci, with dilated vessels and with patches of round cells about them, are scattered through the cortex, and this cannot, I think, be due to local poisoning of the vessels by the products of a special nervous degeneration. It seems to me, from what one knows of syphilis in other organs, that the changes are just as likely to be properly

interpreted by attributing them to the action of the poison upon the vessels in the first instance, causing, in some cases, actual inflammatory lesions round them, and in other instances producing the defective nutrition of the nerve-cells and the irritation of the connective tissue, as they are on the usually accepted hypothesis.

THOMAS BUZZARD

said he felt so little qualified to discuss from intimate and personal knowledge the microscopical revelations dependent on the most recent staining processes, that he should almost have shrunk from rising on the present occasion but for the opportunity which it gave him to express his estimation of the value of the paper and demonstration which they had had brought forward. Clinical observation must largely be concerned in this question of the pathology of tabes and its relation to general paralysis, and it was from that side that he would venture to make a very few remarks. His experience was that mental symptoms might and did, though not very frequently, occur in tabes, but he could not call to mind an instance in which tabes had begun with mental symptoms. He had seen a considerable number of cases of general paralysis which presented symptoms of tabes during life, and indeed had not infrequently experienced great difficulty in determining to which category the case should be allotted; but opportunities had been wanting to him to observe the pathological condition after death in cases of general paralysis, as these usually passed into the hands of the alienist. He would say at once that from a clinical point of view he quite agreed with Dr. Mott, in regarding the evidence that syphilis was the most important factor in the production of both tabes and general paralysis as unquestionable. Dr. Mott's unique experience as regarded juvenile general paralysis appeared to him to present overwhelming evidence as to the dependence of general paralysis on syphilis. And he was also disposed to think that there was sufficient evidence to show that general paralysis and tabes were essentially one and the same disease affecting different parts of the nervous system. An instance

which had occurred in his own practice pointed with remarkable force in the direction of showing the relationship of the two diseases. In 1890 a husband and wife consulted him, both suffering from typical tabes. The man had had syphilis in 1880, and had married within two months. His wife had bubo two months after marriage, and lightning pains six years later. Under specific treatment the husband greatly improved; the wife developed grandiose conceptions of a kind completely characteristic of general paralysis of the insane. She then passed into a stage of maniacal violence, and died in an asylum in the middle of 1891, after a succession of epileptiform and paralytic seizures. As regarded another point proposed for discussion, he was disposed to agree with the view that both diseases could be pathologically considered as a primary decay of the neuron with secondary inflammatory and subinflammatory changes in the meninges and formative proliferation of the glia cells. But he did not think that this was always the order of events, and it was possible that (as he thought occurred in insular sclerosis) the two processes might go on side by side.

Was the toxic influence of syphilis essential for the production of this degenerative process, seeing that in a certain number of cases there was only a history of what was called a soft sore? The infection of syphilis was in his opinion unquestionably the most frequent cause of these diseases, but it had not yet been proved to be the only one. It often, indeed, happened that in a case of tabes one could only obtain a history—though a circumstantial one—of a soft sore. Until other possibilities had been exhausted, to argue that in such a case there must necessarily have been true syphilis mingled with the chancroid, did not appear to him to be quite logical, as it assumed the necessity for the presence of that which had not been proved to be absolutely essential. It was true that the exact nature of the soft sore was still *sub judice*, and the question in what way, if at all, it was related to syphilis was undetermined. In view, however, of the fact that a specific micro-organism had been described by Ducrey, Unna, and Buschke as being present in the soft sore (though not in the syphilitic), it appeared to him premature to put the soft sore out of court as a possible source of a toxin capable of causing the degenerative changes in question. He had suggested this last year in opening a discussion at Edinburgh

on the influence of toxins in the production of disease of the nervous system, and had since been interested in finding that Hitzig had preceded him in the idea, of which he had not been aware when writing his paper. It would be remembered that in multiple peripheral neuritis, a disease characterised by degenerative changes, and which was always of toxic origin, the lesions observed microscopically were essentially the same whatever might have been the particular toxin by which they had been brought about.

Sir William Gowers, F.R.S.

I must first add my tribute to the recognition of the interest of the demonstration, and the ability of the exposition we received from Dr. Mott at the last meeting, and of the proof it affords of the wisdom of the step taken by the London County Council, and of the appointment by which they completed it. I have little to criticise in the statements made by Dr. Mott, and much to endorse in the remarks of Dr. Buzzard. The question of the preponderant relation of tabes to syphilis has, I think, long passed into the region of admitted fact. I have published more extensive statistics on this point, but for the sake of the discussion this evening, I have been through my notes of the last 100 consecutive cases of tabes seen in private, which constitute an unselected series, with this result:—In sixty-eight cases there was unquestionable evidence of past syphilis. In 12 per cent. the disease was probable; there was evidence of a chancre of uncertain nature, making 80 per cent. of certain or probable syphilis. In the remaining 20 per cent. the disease was possible, that is, there had been exposure to the ordinary risks of infection, emphasised in most cases by the occurrence of gonorrhœa, often several times. In not one of the 100 cases could the disease be excluded by the absence of any exposure to risk of its contraction in the ordinary way. We all know by experience that it is only by this means we can actually exclude it, for all have met with such cases as those quoted by Dr. Mott from Dr. Radcliffe Crocker, in which the constitutional disease has occurred without any history of a primary sore. Two of the cases in this series would have gone into the "possible"

class but for the facts that the wife of one suffered from syphilitic choroiditis, and a child of the other from interstitial keratitis. All these cases were males. In the case of women the facts are obviously more difficult to obtain; but evidence of syphilis is, I think, clear in at least half the cases, and the remainder are for the most part married women, in whom the disease notoriously often eludes recognition. It is unjustifiable to inflict on the husbands the distress of direct questions.

In juvenile tabes we seldom have doubt. The evidence of inherited syphilis is usually clear. It was so in about six cases I have seen, and I have met with one instance in which both father and son suffered from tabes, the former from acquired, the latter from inherited, syphilis. Optic nerve atrophy is also sometimes seen in these cases of juvenile tabes. So also is reflex iridoplegia—the Argyll-Robertson symptom. With regard to this Dr. Mott remarks that, apart from tabes, it is only met with in cases of syphilitic brain disease; but I would remind him that ten years ago, in some lectures on syphilis and the nervous system, I pointed out that this isolated loss of the light reflex is not rare in cases of constitutional syphilis apart from any other characteristic nervous symptoms. It is so in men, women, and children, and I would emphasise it because my observations since have confirmed me in the opinion that it is a diagnostic symptom of great weight, and often very opportune.

Few of us are in a position to criticise the facts which Dr. Mott has given us regarding general paralysis and its relation to tabes. My own experience emphatically confirms the statement by Dr. Buzzard, that when the symptoms of the two diseases are associated, those of tabes precede those of general paralysis. I have seen a large number of cases in which the latter supervened on the former; I do not recall any case in which the paralytic symptoms led the way, and the knee-jerks afterwards became lost. The common rule in cases of this class is for the legs to remain normal, or more commonly for an excessive knee-jerk and foot-clonus to accompany progressive loss of power. In the tabetic cases a history of syphilis is, I think, as common, and its presumption as constant, as in the pure cases of tabes; but I do not think that this statement can be made of the paralytic class, although the facts are not easy to ascertain. Of the juvenile cases of general paralysis described by

Dr. Mott I have had no experience. The only instances of the kind I remember have been cases of arrest and irregular impairment of cerebral function, not progressive, associated with the inherited disease, but most readily explained by actual specific disease of the brain.

The pathological questions I must, with Dr. Buzzard, leave to those with whom remains the opportunity for elaborate investigation. Dr. Alexander Bruce does not, perhaps, remember how strenuous, twenty-five years ago, was the advocacy of the dependence of the changes in the posterior columns on the meningitis over them, and on the interstitial and perivascular alterations, although not precisely in the minute form which he suggests. The theory disappeared for a reason which I think still holds good. These extra-neural alterations are inconstant, especially in degree, and they can be equally explained by the secondary neuroglial and vascular alterations which occur whenever there is a primary degeneration of the nerve elements; for example, in that which is secondary to a traumatic process, or focal myelitis. On the other hand, the theory failed entirely to account for the most remarkable fact of tabes, the restriction of the symptoms to function, the manner in which, in the slighter cases, without cutaneous sensory disturbance, there was only degeneration of the fibres of the posterior median columns, which we have learned to regard as the upward path from the afferent muscle-nerves, and the frequent, almost usual, loss of sensation to pain; it may be almost complete throughout the legs, with no impairment of sensibility to touch. There may be, though this is indeed a rare condition, loss of sensation to touch only, limited to the soles of the feet. We cannot explain such a functional limitation by a process essentially random in incidence. All the teaching of our pathological knowledge since has been that such restricted impairment is the result of the action of a toxic blood-state on the nerve elements themselves. Difference in function involves variations in susceptibility, by which slight differences in the nature of the toxic agent, perhaps inconceivably minute, involve effects altogether different in the symptoms produced.

We must remember, moreover, that in the case of other toxic agents the chief effects are produced on the extremities of the nerves, lessening in degree as we approach the centres. I think,

therefore, that we need not be surprised at the slightness of the changes that can be perceived in the cells of the posterior ganglia. If the fibres which conduct from the ganglia are degenerated more completely—may not this be in accordance with a law which we cannot yet understand? We must expect to meet with facts we cannot yet explain.

The question of the identity of tabes and general paralysis as one disease, due to the same cause, acting on cerebral and spinal neurons, seems to me very much a question of words. Does even common causation create identity of diseases which differ so widely in symptoms as the cerebral form of general paralysis and the pure form of tabes? Does the fact of blending forms, and cases with common symptoms, create identity when there is a complete contrast between the extreme forms? If so, we ought to regard a scrofulous tumour of the brain and pulmonary phthisis as one disease, or even erythema nodosum and the acute articular rheumatism which may coincide with it. But would this correspond with our common use of the term "disease," which is connected with a definite aggregation of symptoms rather than with their discerned causation? This statement may, however, be regarded by Dr. Mott as handing to him the point at issue. It does, I think, so far as concerns the cases of tabetic general paralysis, but the cases of the paralytic form seem open to more question, which I must leave to Dr. Savage to solve. I would point out how imperfect is our present nomenclature by which we have to speak of tabetic and paralytic general paralysis. The German term, "paralytic dementia," has never obtained a foothold here, the word "dementia" having different associations. I do not know that any other word, such as "paramentia," would be appreciably better.

The final question put by Dr. Mott raises a problem of great importance, on which I have long held a decided opinion. Dr. Mott asks whether the toxic agent "does not lower the durability of the nerve elements, so that some other factor" inducse a premature decay. I have long maintained that this is an essential secret of the mysterious incidence of these degenerative diseases. An average man inherits an equal vitality in all his structures. He goes to pieces at last like the famous "one-hoss shay," all at once, in mature, equable, senile decay.

At the other extreme are those individuals who possess structural elements (it may be in some part of the nervous or the muscular system) so deficient in vital endurance that they decay as soon as, or soon after, complete development is achieved.

Such are some cases of idiopathic muscular atrophy, of congenital atrophy of the optic nerves, in which sight fails in a whole family soon after puberty, or of "hereditary ataxy,"—"Friedreich's disease," in which certain structures of the nervous system decay soon after adult age is reached. In other cases the defect in vital endurance is only sufficient to render some structures less resistent than others; to cause, for instance, the motor nerve structures to decay before the others under the influence of grief, or the nutrition of the cerebral structures to give way under the strain of work or anxiety. This disposition to decay, sometimes inherent, strongly or slightly, seems to be induced artificially by toxic and perhaps other influences. Their effect is specific in many cases, probably in more than we can discern. They lead to failure of nutrition, decay, degeneration. It may seem spontaneous, or be evidently excited. It may occur soon, a few years after its cause has seemed active, or the effect may be only manifest so long afterwards that the connection may be perceptible solely by these considerations. Thus tabes may be a post-syphilitic disorder in middle life, or only, yet with the same relation, when the general failure of approaching age obscures the significance of the cause. We shall understand many things more clearly if we perceive that acquired influences may have the effects of congenital dispositions, that either may cause effects unaided, and may predispose to the results of influences that would otherwise seem to act alone. These considerations are, I fear, somewhat beyond the question before us, but they are not, I think, beyond its indications.

G. H. Savage.

In considering the pathology of tabes and general paralysis, and their relationship, one thinks in the first place of the double connotation of the word pathology; there is the living process, and the morbid anatomy. The two diseases resemble each other

most strongly, as has been pointed out, in the sex and the age at which they are most common, the social conditions under which they most frequently occur, and their frequency in connection with syphilis, as well as in the changes met with after death. I would say at once that my experience, which of general paralysis is very large and of ataxia not so large, leads me to agree with everything Dr. Mott has said; and the more I see and the more I am able to investigate the history of these cases, the more clearly does it come out that syphilis is certainly one of the most important elements. We have, however, to be cautious in drawing conclusions too readily. Probably both general paralysis—of which I speak most from knowledge—and tabes depend upon some toxic influence, some influence that interferes with nutrition of nerves and muscles. And yet one knows that similar symptoms to those which occur in general paralysis of the insane are produced by other toxines—I might say toxines which act in direct relationship to their stability or their specificity; that, for instance, the symptoms which we meet with in general paralysis, and also in tabes, are not uncommonly met with as the result of alcohol; that a more stable poison still, that of lead, produces similar symptoms. And then one has to point out that some poisons or some conditions, whatever term you prefer to use, such as the producer of influenza and the producer of syphilis, seem to have specific effects upon the most unstable and highly developed parts of the nervous system. One has to remember, therefore, that in the consideration of any toxic influence we must be prepared to find similar symptoms, and not lay too much stress on likeness of symptoms alone. Therefore I agree with what Sir William Gowers said, that we should almost want a fresh definition of the word disease if we were to put together all such affections as have a common cause. Seeing that similar influences, or causes, such as toxines, affecting the highest nerve-cells produce similar symptoms, one may expect that anything affecting these cells to their destruction will produce similar clinical results. It does not matter very much whether the house is set on fire by dynamite or by a paraffin lamp, the wreck will be just the same. So one would be inclined to say we must not pay too much attention to the pathological débris; one has to look upon the clinical pathology as well as the débris that results from the morbid changes. Of course I recognise

that in this work which Dr. Mott is doing, as well as others, the investigators are not content with débris; they are tracing the origin as well as the result of the fire as carefully as they can. My experience leads me to think there is no doubt that syphilis is a very potent factor in the production of both general paralysis and locomotor ataxy. I now ask myself, "What are the more common relationships between the two with which I have met?" First of all, I have seen many patients who have suffered from all the symptoms of locomotor ataxy for years, even as long as nine, and have then developed true general paralysis of the insane, ultimately dying of the latter disease. I have met with cases, on the other hand, in which both the symptoms of general paralysis and ataxy have come on coincidentally, and have run absolutely parallel courses. But I must add that I have seen other cases in which there has been a kind of alternation, to which I would refer later. Then as to the relative frequency of ataxic symptoms in general paralysis of the insane. On looking through several hundred cases I have found that undoubtedly the larger proportion of general paralytics were not ataxic; in my experience it would not be more than one fifth of the whole who have exhibited ataxic symptoms.

But the general symptoms of locomotor ataxy in general paralysis are clear and indistinguishable from those of true ataxy; so that the various symptoms which occur with locomotor ataxy occur with the general paralytic, who has also ataxic symptoms. In a few cases I think I have seen general paralysis, with some exaggeration of knee-jerks at all events, pass later into conditions of ataxy. Certainly that was so in one case in which there were exaggerated reflexes on one side, and absence of reflexes on the other. And perhaps I may here throw out a suggestion which has appealed to me for many years, which, however, I give only for what it is worth. I used to notice in the *post-mortem* room that in patients who had exhibited very exaggerated reflexes, and who had had spastic paralysis, there was very commonly marked cortical degeneration over the parietal areas; and in those cases there were also marked changes in the lateral columns of the cord. Is it not possible that we many have a cerebral locomotor ataxy; a locomotor ataxy in which some area not as yet mapped out, which is in direct rela-

tion with the posterior columns, is affected at the same time? For it seems to me unlikely that we should have cases of general paralysis in which there was local cortical trouble associated with local changes in the cord; and that on the other hand we should meet with cases in which there were marked and consistent changes in the posterior columns, without there being some definite part of the brain or cortex affected. But this is merely a suggestion that there are probably primary cases of cerebral ataxy. And here, perhaps, it may be well to adduce other evidence to that effect. I have noted alternation in some ataxic cases. In some, locomotor ataxy is very pronounced, and general paralytic symptoms fairly pronounced as well. Then comes a change. The maniacal excitement, the grandiose ideas, have passed off, and the locomotor ataxic becomes extremely feeble upon his legs. With the mental calm there has been a distinct loss of power. On the other hand, the man becomes again maniacal and at once strong and firm on his legs. One individual of that kind when I was playing at rackets at Bethlem Hospital was only too glad to pick up the balls for me during the excitable period; but when he became depressed he was quite unable to get about at all satisfactorily. I know an ataxic patient who again quite recently has been passing through a stage of acute mania. He had when seen by Dr. Hughlings Jackson twenty years ago, all the symptoms of locomotor ataxy. He has passed the greater part of his life in placid paralysis, but periodically has outbursts of mania, during which he becomes extremely restless and excited, and able to walk ten miles with impunity. It is interesting to see that there are some of these cases in which there seems a relationship which has not as yet been made clear, between the cerebral condition and these ataxic symptoms.

There is one other point which seems to me very important. I do not think that Dr. Mott in any way infers that an ataxic person who becomes insane should necessarily become a general paralytic; that, of course, is not true. I have seen one patient from time to time for fifteen to twenty years; he was originally a patient of Sir William Gull, and has been in a private asylum for twenty years. That patient is a typical sufferer from locomotor ataxy, and has been insane the whole time, with varying delusions throughout. I would say, my experience is that you

may have locomotor ataxy with symptoms of insanity of almost any kind. I have seen *crises* of a maniacal type lasting a few hours and passing away, as well as an insane interpretation of any one of the ataxic symptoms; a person *e. g.* having lightning pains has accused his neighbours of having galvanic batteries in the next room; another man has said his neighbour was converting his legs into lightning conductors; another, having a gastric crisis, said his wife was poisoning him with arsenic; another having symmetrical articular disease about the ankles and bullæ about the feet, said the devil had taken a personal interest in him, and these were devil's grips. I mention these cases to impress the fact that there are a fair number of patients who suffer from locomotor ataxy who do not become general paralytics, but who have insane symptoms; the insane symptoms not infrequently being the outcome or the interpretation—the insane interpretation—of the pains.

I wish I could refer here definitely to another matter, but that I cannot do so is the fault of my memory. Many years ago, in a French work, I came across a statement drawing attention to the frequency of a neurotic inheritance among the ataxic; and further it seemed to the author that the neurotic person who contracted syphilis was much more likely to have locomotor ataxy than to have general paralysis of the insane. At all events it is an interesting thing, *if it be true*, that the locomotor ataxic should so frequently have a neurotic inheritance; whereas on the other hand the general paralytic shows comparatively rarely a similar inheritance.

Then as to one other point which has always seemed to me of great interest in the relationship of these two diseases. Of course we get general paralysis much more rarely among women than among men; and among women who have general paralysis I would say it has been my experience to meet with very few indeed presenting ataxic symptoms.

And now in reference to Dr. Mott's questions. I am doubtful about general paralysis and ataxia being the same disease, though I fear, as I said just now, I should find an initial difficulty in defining the diseases. I believe they have a very clear relationship with syphilis. In reference, again, to another of Dr. Mott's questions, I would say that syphilis, in a very large proportion of cases, prepares the ground. It is my favourite

clinical simile for students that syphilis is like the ripening of the pear:

> "And so, from hour to hour, we ripe and ripe,
> And then, from hour to hour, we rot and rot;"

It takes a very little blow or injury to set the ripe pear rotting. And so the syphilitically prepared brain requires some other, probably slight, causes to produce the breakdown. Whether that is also true of locomotor ataxy I am afraid I am not in a position to say.

As to the relationship of these diseases to the decay of the neuron, I feel with Sir William Gowers as I felt with Dr. Buzzard, that, a quarter of a century having passed since I worked very hard with the microscope, things have progressed so markedly that we have to accept the work of such true investigators as Dr. Mott. I say his theory seems to me almost confirmed that there is a primary decay of the neuron, that there is a secondary degeneration, and that the secondary degeneration depends upon some local inflammation brought about by this disease.

Regarding the soft sore and the relationship that may hold to general paralysis or ataxia, I have seen a good number of cases in which the only history one could get was the fact of the existence of such a sore; but, again, I would say my experience is that in nearly all cases of general paralysis there is a history of syphilis with but slight secondary symptoms. Whether the peripheral changes alone can lead to the central decay I cannot say, though it has long been a favourite belief, especially in France.

David Ferrier, F.R.S.

I have been much impressed by the facts and arguments adduced by Dr. Mott in his address, and fully set forth in his Claybury Asylum Report, in favour of the view that general paralysis and tabes are essentially the same disease affecting different parts of the nervous system; and that they are both conditioned by the same cause, namely, syphilis, hereditary or acquired. This is the provisional conclusion at which, in com-

mon with many other neurologists, I have myself arrived as the result of my own clinical observations; and this conclusion is more than supported by the very important fact that Dr. Mott has found evidence of inherited syphilis in almost all the twenty-two cases of juvenile general paralysis which he has had the good fortune to investigate. This is of similar importance to the observations of Krafft-Ebing, to the effect that general paralytics are insusceptible to inoculation with the syphilitic virus. Facts like this are, to my mind, of much more importance, than the evidence of syphilis that one can obtain by questioning patients themselves. For it has been found by syphilologists in cases of diseases of the skin and other affections undoubtedly syphilitic, that in only a certain percentage of these can a history of syphilis be obtained. According to Hirschl, in thirty-six cases only out of every hundred is it possible to obtain evidence of syphilis in cases of that type. Now, if this is so in respect to affections of the syphilitic origin of which there is no question, we need not doubt the syphilitic origin of general paralysis, even if we cannot obtain clear evidence of syphilitic infection in every one of the patients under investigation. Some patients are quite honest in stating that they are not aware of having had syphilis. Others, from their mental condition, are unable to give us any trustworthy information, and not a few wilfully conceal the fact. Of this I have had repeated experience; for I have been told, not infrequently, by patients that they have not had syphilis, when I have been informed from other sources that they have actually been treated for it. So much for the importance of the evidence obtained from the individual. But, notwithstanding all these difficulties in arriving at the exact truth, we have evidence of antecedent syphilis, certain or highly probable, in 81 per cent. of the cases investigated carefully by Hirschl. Some have placed the percentage much higher, others lower. I have taken the trouble to look over cases of which I have notes, chiefly in the ordinary routine of consultation practice, and during the last few years I have notes of seventy cases, of which I find that 67 per cent. certainly had syphilis, and that 8 per cent. probably had, making 75 per cent. in all. Only 14 per cent. denied all syphilitic infection; but, on the grounds already mentioned, I think that these 14 to 20 per cent. may be discounted and that we may, without much risk of error, go the

full length of saying, "No syphilis, no general paralysis." All the assumed causes of general paralysis, such as stress and strain, alcoholic and other excess, included in the comprehensive term "civilisation," have all been by themselves tried and found wanting by Hirschl in his masterly analysis. The largest percentage of general paralysis occurs amongst artisans; and it is my own experience that general paralysis occurs as often among those who have led comparatively uneventful lives as amongst those who have been subjected to the stress and strain of brain work and anxiety. I should regard civilisation as a comparatively unimportant factor, and syphilisation as the essential, without which all the other causes are inadequate. And what is true of the ætiology of general paralysis, holds, I think, with regard to tabes. But why in the one case the cortex cerebri should be affected, and in another the posterior columns of the spinal cord, is a question on which we require further light. That the two affections do occur together in a certain proportion of cases is admitted, but the percentage is, I think, not a large one. Dr. Savage places it much higher than appears from my own investigations. I would place it at not more than 15 per cent. But even this relatively small degree of conjunction is of great significance. Judging by the number of cases of tabes as compared with those of general paralysis occurring in the ordinary course of consultation practice, I should say that tabes occurs three times as often as general paralysis. Thus in the same period of which I have notes of seventy cases of general paralysis, I have particulars of over two hundred cases of tabes.

The pathological process in both cases is a sclerosis, whether this is to be regarded as an inflammatory process or not. I will not venture to express a positive opinion on the vexed question whether the degeneration is primarily parenchymatous or primarily vascular and interstitial. There is much to be said on both sides. But there is one fact I should like to mention, which I think is of importance in this connection, viz. that the process which leads to the adhesion of the membranes and hyperplasia of the interstitial tissue is a painless one. In this it differs strikingly from meningitis, whether specific or non-specific. The absence of pain in the head on percussion, or deep pressure, in general paralysis, is a noteworthy feature which I am in the habit of pointing out in my clinical demonstrations. This

contrasts strikingly with what occurs in the cortical affections characteristic of cerebral syphilis, where, even if pain is not spontaneously complained of, deep pressure over the affected area seldom fails to elicit distinct evidence of it. And in doubtful cases I am in the habit of regarding the presence or absence of pain on pressure of the skull as a valuable diagnostic aid in distinguishing between cerebral syphilis and general paralysis, which often, in their early stages, so closely resemble each other.

J. F. PAYNE.

I feel that when I undertook to make a few remarks on this subject before reading the abstract of Dr. Mott's paper, I committed a rash action; as having no special experience in nervous diseases, if apologies were needed at all to-night, they are especially needed by me.

But I think that Dr. Mott's paper, and especially his specimens, are most important contributions to the pathology of the two diseases which have been spoken of; and more especially so because, although this question has been raised before, histological evidence has been either defective or extremely conflicting. We know that Fournier, in his lectures on Parasyphilitic Affections, says that persons began by saying that general paralysis and tabes were affections very nearly related; next, that they were cousins; other bolder theorists alleged they were sister diseases, and now, he asks, why not take a further step and say they are the same disease? Fournier, in his anatomical discussion of the subject, says there is a serious gap in his argument, because he has not been able to get anything definite from the statements of histologists. For that reason Dr. Mott's paper is exceedingly valuable. I am not sufficiently familar with the recent methods of histology to be able to criticise his specimens, but they seem decidedly convincing. There is one point on which he seems at variance with some pathologists, that is as to the relation in point of time and causation between the degenerative changes in the nervous system and those vascular and connective-tissue changes which are called sclerosis. Dr. Alexander Bruce seems to lean to the view that the nervous

degenerations are secondary to certain morbid processes in the blood-supply and the connective-tissue structures of the parts affected.

It is generally admitted that by a simple histological examination it is almost impossible to arrive at an exact conclusion, since we see the two changes side by side, and cannot at once say which was the primary morbid process. But in supporting Dr. Mott's view, I rely on this fact: that there are certain diseases, or rather certain morbid conditions, in which it is absolutely demonstrable that the nerve degeneration is the primary change, and the connective-tissue growth and vascularity secondary. I may refer to the evidence given by experimental section of nerve-roots for instance. On the other hand, there is not a single case known to me in which the converse can be established or proved; that is, in which the connective-tissue and vascular changes can be absolutely demonstrated to be primary, and the corresponding or accompanying degeneration demonstrated to be secondary. Therefore I think the neutral or ambiguous cases should be interpreted by those in which the order of the morbid processes is definitely established; and we are justified in saying that very generally, if not quite universally, the nerve degeneration precedes the connective-tissue growth and vascular disturbances in such diseases as tabes and general paralysis.

With regard to the dependence of these two diseases upon syphilis, I suppose few members of this society doubt that the connection is very close, though perhaps this may not be generally admitted in the profession. I have no pretension to give statistics on this subject, because my experience is far too limited; but I mention one fact which I think every one must admit, namely, that in those cases, more especially perhaps of general paralysis, but also of tabes—unfortunately occurring in professional men, including our own profession—with which we are personally acquainted, evidence of syphilis is generally forthcoming. Certainly, such cases as I have known at all intimately, have left no doubt in my mind that the disease was due to syphilis. Therefore, in those cases in which our relations are purely professional, and in which our opportunities of obtaining confidential information are less complete, the probability is that there would also be evidence forthcoming, if all the

information were before us, that the two diseases are both due to syphilis. If this be true, a large part of Dr. Mott's contention would be proved.

I remember when the view was first put forward great difficulty was felt, especially by morbid anatomists, in admitting that a disease which produced other affections totally different could be responsible for these diseases; because syphilis generally speaking produces either active inflammations or degenerations of a focal nature, not diffused organic disease. But then, again, not only in these particular nerve diseases, but in diseases of other organs, we have had to go through the same process of unlearning some of our prejudices. For instance, in cirrhosis of the liver I remember the time when no one would admit that syphilis could be the cause of a diffuse cirrhosis of the liver. We recognised syphiloma of the liver, and thought the same cause could not possibly produce an affection so different from this as diffuse fibrous inflammation. But first, it was proved beyond a doubt that hereditary syphilis does cause cirrhosis in children, though one anatomically different from that due to alcohol. Then one had to go back to cases in adults where there was a history of syphilis together with one of alcoholic excess, and though alcohol might also be a factor, it was necessary to admit that in many cases the syphilis was the main cause, or at all events a large one. I will not go into this subject fully now, but the same is true of a peculiar form of renal disease, *i. e.* those remarkable cases of cirrhotic granular kidney occurring in children, which have always been regarded as rather a stumbling block in the accepted theory of this form of Bright's disease. Dr. Sibson used to say he could not make those cases out at all. From various cases I have seen, I certainly believe that most of these—I cannot say all—are due to inherited syphilis. This is another instance of the syphilitic poison producing diffuse general inflammation as well as focal inflammation and degeneration. These diffuse diseases, of course, cannot be produced precisely in the same way as the others, that is focal syphilitic affections. We must assume that some sort of diffusible toxic substance is generated or in some way produced by the unknown microbe of syphilis which causes these diffuse affections. I have been in the habit, by way of explaining matters to students, of calling them post-tertiary

syphilitic affections. But the term introduced in the classical lectures of Dr. Fournier—parasyphilitic—is likely to be more generally accepted. Whether they be post-tertiary or not, they are different from the ordinary syphilitic diseases, secondary or tertiary.

With regard to nervous diseases, I am going—with all respect to the neurologist—to make a suggestion, namely, that there is another so-called systemic disease, *i.e.* primary lateral sclerosis, or primary spastic paraplegia, which is far more often due to syphilis than is generally supposed. I have seen some exceedingly well-marked cases, and it is a peculiar feature that this may be at times, what the others are not as a rule, amenable to treatment. I cannot enter into this subject now, but I believe it may be found that a diffuse syphilitic toxine affects the upper segment of the motor tract as well as the ascending tracts, or the cortex of the brain.

Some pathological evidence may also be derived from the influence of drugs, which I venture to refer to, though not in its practical bearing. I may mention that I had as a patient a woman in whom there was no doubt lateral sclerosis, or at all events spastic paraplegia of a most pronounced type, in which I made the supposition that it was due to syphilis. She was treated with iodide of potassium, and she got well, and is now a healthy and hearty woman. The curious fact, however, was not that she got well, which might be explained in various ways, but that during the process of recovery she had an affection of the eye. She was sent down to the eye department of the hospital, where the affection was diagnosed as undoubtedly syphilitic iritis, that being a syphilitic affection belonging to the secondary stage, whereas the nervous disease was a post-tertiary or the latest stage of all. I have seen an exactly similar thing in another case, that of a boy, who afterwards died. He was one of Dr. Mott's group of infantile paralysis, his affection being what was formerly called cortical sclerosis. That boy also was treated with iodide of potassium, with only partial success, but while under treatment he also developed syphilitic iritis. The supposition one would make is that the toxine or antitoxine produced in the latest stages of syphilis by the operation of the original syphilitic virus has an inhibitory effect, so to speak, on the disease; for it is remarkable that the subjects of parasyphilitic nerve

diseases do not as a rule show focal inflammatory syphilides. There is some plausibility about the supposition that such an antitoxine inhibits the further progress of the disease. The giving of iodide of potassium seems to inhibit the action of the antitoxine, to set free the evolution of the disease, so that it then reverts to an earlier or secondary stage. This is, I admit, a somewhat rash hypothesis, but I venture to put it forward as material for consideration.

W. Hale White

said that he had heard with very great pleasure the address which Dr. Mott had given, for he had been accustomed for some years to teach the same views as Dr. Mott had expressed. It appeared to him that the most reasonable opinion to hold was that a person once having had syphilis was therefore more liable than others to become the victim of a chronic morbid process such as Dr. Mott had described, and that it might attack any part of his nervous system, but that it particularly first attacked one of two parts—namely, either the grey matter of the cerebral cortex, or the posterior nerve-roots of the lumbar and lower dorsal cord central to the ganglia. In the first instance the disease was comparatively rapidly fatal, because of the large amount of nervous tissue involved, this probably acting, as Dr. Mott had suggested, partly through absorption of toxic products of disintegration of nervous tissue. In the second case the disease lasted longer, and was naturally followed by a degeneration in the posterior columns, as in the first case it was succeeded by a degeneration of the lateral. It followed from this view that, as Dr. Mott had said, often the two types were combined in the same patient at some period of his illness, and it also followed that if a patient came before them with what appeared to be ordinary tabes, but as the disease went on the observer was struck by the rapidity with which it developed, then he could almost certainly predict that it would ultimately turn out to be of the general paralytic type. He had often found this true, and of great value in prognosis. But he regarded it as essential to remember that while there were two great clinical groups in which the result of the syphilis was manifested, either

in the cortex of the brain or in the lumbar and dorsal posterior nerve-roots central to the ganglia, so there were cases in which the first effect was seen in the peripheral nerves, such, for instance, as those in which the first symptom of tabes was either an ocular paralysis, laryngeal paralysis, or even paralysis of some other muscles. In these cases it seemed reasonable to assume that the peculiar syphilitic result now under discussion was shown first in certain of the peripheral nerves; in those cases in which optic atrophy was the first symptom of the disease, it was shown in the optic nerve. He said it was no refutation of this view to say that it was unlikely that the same cause would damage sometimes one part of the nervous system and sometimes another, for other poisons, such as lead, did the same. Perhaps the reason for this selective power of poisons and the toxines of specific fevers was to be sought in slight chemical differences in the composition of the tissues. He quite agreed with Dr. Mott that general paralysis and tabes were most often seen in those in whom the earliest symptoms of syphilis had been slight.

F. E. BATTEN

[With Plate XI.]

recorded the examination of a case of tabes with special reference to the condition of the sensory nerve terminations in the muscles.

The case clinically was a well-marked one of tabes and general paralysis, and the following was a brief abstract from the notes.

S. G—, aged 45, was admitted to the National Hospital on December 31st, 1897, under the care of Dr. Ferrier, to whom the speaker was indebted for permission to make use of the notes of the case.

The patient had been married eleven years; his wife had had five healthy children, the youngest of whom was two years old; there had been no miscarriages.

Syphilis was denied, but the patient had had gonorrhœa twenty-five years previously. Four years before admission he had worked for an army examination, which he passed successfully, and continued to study until "he broke down in his legs."

Three years ago his legs became gradually affected so that he did not know how to put his feet down, he had girdle pains, shooting pains, and frequent micturition.

Two and a half years ago he had a fit and has continued to have these at intervals, at first about every two months and latterly about every week. During the fit he was unconscious, bit his tongue, struggled on the floor, and in one of these he lost his speech for a time.

One year ago his memory began to fail and he lost sexual power.

On admission the patient was mentally confused and unable to talk coherently; his memory was very bad. There was slight ptosis of the left eyelid; he had Argyll-Robertson pupils, but no squint or diplopia. He had analgesia as high as the knees; his gait was very unsteady and ataxic. The knee-jerks were absent, but the plantars and abdominal reflexes were present. The patient died rather suddenly of respiratory failure. The autopsy showed thickening of the pia arachnoid over the surface of the brain, wasting of the convolutions, and compensatory œdema. There was thickening of the meninges over the dorsal and lumbar aspect of the cord, but the cervical region was almost free.

Microscopical examination of the cord showed well-marked sclerosis of the posterior columns, leaving however the cornu-commissural zone and the septo-marginal tract intact in the lumbo-sacral region, and the column of Burdach much less affected than the columns of Goll in the cervical region. Lissauer's tract was markedly affected in the lower levels of the cord, but was comparatively free at the higher levels. The posterior nerve-roots were most atrophic in the lower dorsal and lumbar regions, only a few fibres staining by the Weigert-Pal method, and only a few axis-cylinders by the Stroebe method. The vessels lying in the roots of the dorsal and lumbar regions were markedly engorged. In the cervical region the roots were only slightly affected.

The posterior root-ganglion showed marked change by the Nissl method, many of the cells being shrivelled and extensively pigmented. When stained by Stroebe's method the change described by Dr. Mott, *i. e.* the different coloration of ganglion cells, in the posterior root-ganglion cells could not be seen, and by Van Giesson's method the increase of con-

nective tissue between the cells and also in the posterior nerve-roots was a marked feature.

The anterior and posterior branches of the nerve as they left the ganglion showed very little change either by the Weigert-Pal, Stroebe, or Van Giesson method; but the contrast between the anterior and posterior root in the neighbourhood of the ganglion was very striking.

Method of examination.—The examination of the nerves was carried out by the Marchi, Weigert-Pal, and Stroebe methods; the examination of the muscles by the Marchi, Weigert-Pal, and Van Giesson methods; whilst the muscle-spindles were examined firstly by Sihler's method, and subsequently, after hardening in Müller's fluid, by the Marchi and Weigert-Pal methods.

Portions examined.—The parts especially examined were the anterior crural nerves and the branches to the vastus internus, rectus femoris, and vastus externus muscles, the finer branches of the nerves in the muscles mentioned, and the nerves passing to the muscle-spindles. The sciatic nerve and the larger and smaller branches of the anterior tibial and some muscle-spindles from the abductor pollicis were also examined.

Nature of change found.—Nerves: The peripheral nerves showed very little departure from the normal by the Weigert-Pal method; with the Marchi method, however, the medullated sheath in certain scattered areas showed slight fatty change, but it could not be said that the finer nerves as they enter the muscle show any more marked change than the larger nerves. The anterior crural nerve showed more change than the sciatic, but in neither nerve was the condition marked, and the axis-cylinders when stained by Stroebe's method appeared normal; the only alteration to be noted by this method was that the medullated sheaths of the nerve tend to stain irregularly. The nerves supplying the muscle-spindles were normal.

Muscle-spindle: When the muscle-spindle is stained by Sihler's method and is teased out, the nerve passing to the spindle, the sheath of the spindle, and the intra-fusal[1] muscle-fibres appear normal. When, however, the muscle-spindle, after being hardened in Müller's fluid, is stained by Marchi's method,

[1] The terms intra-fusal and extra-fusal are those suggested by Professor Sherrington, derived from "fusus" a spindle.

it is found that the intra-fusal muscle-fibre showed marked fatty degeneration, and this, although it might exist along the whole length of the muscle-fibre within the spindle, was most marked on either side of the equatorial region, where it has been shown that the muscle-fibre undergoes such modification that the transverse striation normally is absent. The striation of the muscle-fibre was still present in that portion of the muscle-fibre that showed the fatty change. The condition is shown in Pl. XI, fig. 2, from a photograph of a longitudinal section through a spindle. The extra-fusal muscle-fibres showed no fatty change.

With regard to the change above described various explanations suggest themselves. (1) It is a normal condition; it is not however, found in the spindle of a normal man, nor is it found in any of the following conditions:—infantile paralysis, myopathy, progressive muscular atrophy; it is not present in the muscle-spindle of the dog, nor can it be artificially produced by the section of the nerve supplying the muscle. (2) It is an acute change occurring shortly before death, similar to the changes described by Dr. Mott in the muscles of patients dying in status epilepticus, and the present case is certainly open to criticism on that ground, since it was a case of tabes associated with general paralysis of the insane and epileptic convulsions. There is no reason to believe that it is due to an acute toxic blood-state, since the change is limited to the intra-fusal muscle-fibres, and had it been due to this cause it is certain that other muscle-fibres would have been affected. (3) That it is a pigmentary change similar to that found in the cells of the anterior horns and posterior root ganglia under various conditions, but especially in those of old persons. Further evidence is yet needed on this point, and it is not certain that such pigment may not indicate some morbid change in the cell body. The change would, therefore, seem to be a degenerative one; but since the nerve supplying the spindle may be normal when the change is present in the intra-fusal muscle-fibre, the assumption that changes may occur in that portion of the neuron most distant from its trophic supply, before they manifest themselves in the intermediate portion, would seem the most ready explanation. The change above described is fairly constant in tabes; it was present in a case of tabes unassociated

with general paralysis which I described in a former paper on the muscle-spindle,[1] and it was present in all the spindles of the present case examined from the vastus internus and rectus femoris, but was not present in those from the abductor pollicis. That the muscle-fibres, although showing the fatty change, should retain their transverse striation is not so anomalous as might at first appear, for it has been shown by Sherrington[2] and Horsley[3] that the intra-fusal muscle-fibres retain their striation, and do not atrophy even after the nerve supplying them has been divided for many months. It has been shown that the muscle-fibre within the spindle is of the variety known as "red," and further, it is known that after section of a nerve white muscle-fibre atrophies much more rapidly than red. It is possible that one has here a form of muscle-fibre which is still less dependent for the maintenance of its nutrition on its nerve-supply.

Details of Examination.

Anterior crural nerve.—By the Marchi method the medullated sheath of many of the nerve-fibres appeared normal; some have, however, undergone slight fatty degeneration. The degeneration was seen both in longitudinal and in transverse section of the nerves; in some fibres it affected the outer portion of the medullated sheath, in others the inner portion, and in others the sheath itself.

Nerve to the vastus internus muscle.—By the Marchi method the same slight changes that were seen in the anterior crural nerve were present also in this nerve. By the Weigert-Pal method the medullated sheath of the nerve presented a somewhat granular appearance, but otherwise appeared normal, and no pathological signification could be attached to this granular appearance.

Nerve in the vastus internus muscle.—By the Marchi method no change could be shown in the nerves within the muscle, and by the Weigert-Pal method the finer branches of the nerve appeared normal.

[1] Batten, 'Brain,' 1897, p. 164.

[2] Sherrington, 'Journal of Physiology,' vol. xvii, p. 246.

[3] Horsley, 'Brain,' 1897, p. 375.

The vastus internus muscle examined by the two former, and also by Van Giesson's method, appeared normal; the extra-fusal muscle-fibres measured from ·05—·08 mm.; the transverse striation was well preserved, and the muscle-spindles as seen on transverse section appeared normal, both in regard to their sheath and intra-fusal muscle-fibres (Pl. XI, Fig. 1).

Muscle-spindles in vastus internus muscle.—The spindles were teased out of the muscle by Sihler's [1] method, and by this method the spindle itself, its contained muscle-fibres, and the nerve-supply appeared normal, and in some spindles no less than four distinct nerve-bundles could be traced entering the spindle.

The spindles after being teased out were hardened in Muller's fluid and in Marchi's fluid, and having subsequently been passed through the necessary media were embedded in celloidin, and cut in longitudinal section in series. Some of these spindles were now stained by the Weigert-Pal method.

The specimens stained by this latter method showed that the nerves passing to the spindle were normal. Fine nerve-fibres branched off from the main trunk before it reached the spindle, and these could be traced to the extra-fusal muscle-fibre; the larger nerve-fibre, which is known to pass to the equatorial region of the spindle, could be seen and traced within the spindle, but although the nerve to the spindle was natural in this respect, yet there seem to be fewer nerve-fibres within the spindle than normal.

The spindle when examined by the Marchi method showed a very marked fatty degeneration of the intra-fusal muscle-fibre, and this, although most marked about the equatorial region of the spindle, might in some spindles extend the whole length of the intra-fusal fibre. The nerve passing to the spindle showed no change; it might however be argued that the products of degeneration had been absorbed, and therefore no change would be visible by the Marchi method; the staining of the nerve by the Weigert Pal method however negatived such a suggestion.

[1] The details of the method are fully given in a former paper on the muscle-spindle published in 'Brain,' 1897, and it may be well to point out here that the only fallacy in the use of this method is due to the fact that as the muscle-spindle is most easily recognised by its nerve-supply, the tendency is to tease out the more normal muscle-spindles; and therefore one has endeavoured to tease out all the muscle-spindles in the part of the muscle examined, and in this way to diminish any error that might arise.

DESCRIPTION OF PLATE XI.

Illustrating Dr. F. E. Batten's contribution to the Discussion on the Pathological Unity of Tabes and General Paralysis. (Page 369.)

FIG. 1.—Transverse section of a muscle-spindle from the right vastus internus in a case of tabes. Magnified 100 times. The extra-fusal muscle-fibres are of normal size, and average about ·06 mm. in diameter. The intra-fusal muscle-fibres, seen in the centre of the figure, are eight in number, and of about normal size (from ·008 mm. to ·02 mm. in diameter). The muscle-spindle has evidently been cut near its equatorial region, judging from the considerable number of intra-fusal fibres and the wide lymph space between the muscle-fibres and the sheath. The sheath of the spindle is well defined; in close proximity to it on the left is the cross-section of a nerve. The central nucleus of the intra-fusal muscle-fibres is clearly visible. (Stain, hæmatoxylin.)

FIG. 2.—Longitudinal section of a muscle-spindle from the right rectus femoris in a case of tabes. Magnified 100 times; showing fatty degeneration of the intra-fusal muscle-fibres. If the muscle-fibre against which the letter *b* is placed be traced towards the centre of the figure it will be seen to contain numerous fat droplets, stained black by osmic acid; as it is traced still further to the left the transverse striation of the fibre becomes interrupted, and nuclei are evident in the centre of the fibre (as is normal at the equatorial region of the spindle). The letter *a* is placed against the sheath of the spindle, the letter *c* against an extra-fusal muscle-fibre, the letter *d* against an arteriole. (Stain, Marchi.)

Both the figures are from microphotographs.

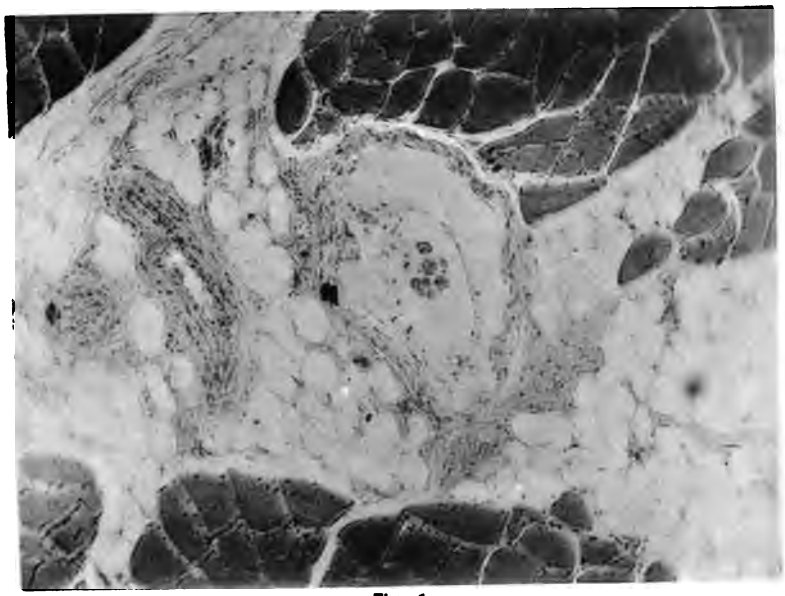

Fig. 1.

Fig. 2.

The muscle-fibre, in spite of the fatty change, frequently retained its transverse striation.

Nerve to the right rectus femoris muscle.—By the Marchi method the finer nerves passing to the muscle showed only a slight change, similar to that described in the anterior crural nerve.

By the Weigert-Pal method the finer nerve-fibres appeared normal.

Muscle-spindles from the right rectus femoris.—In the teased specimens (Sihler's method) the nerve-bundle passing to the spindle appeared perfectly normal; it could be seen to enter the spindle, and the finer branches passed towards the poles, while the larger nerve-fibres end on the muscle-fibre in the equatorial region. The striation of the intra-fusal muscle-fibres was well marked.

Spindles examined by the Marchi method show very marked fatty degeneration of the intra-fusal muscle-fibre. The degeneration, as in the spindles from other muscles, was most marked in the equatorial region, although it did not affect that portion of the muscle-fibre in immediate contact with the nerve termination. The nerve supplying the spindle appeared normal, and no change could be seen in the extra-fusal muscle-fibres.

Spindles examined by the Marchi-Pal method show that the larger nerve-bundles, and also their finer divisions passing to the spindle, were normal; the fatty change in the intra-fusal muscle-fibres was present in these specimens also.

Nerve to the right vastus externus.—The same slight change, seen in the nerve to the other muscles was present in this nerve and its finer branches; the axis-cylinders, when stained by Stroebe's method, appeared perfectly normal.

The right sciatic nerve appeared normal by the Marchi-Pal method, and showed only very slight change by the Marchi method.

The right anterior tibial nerve showed slight degenerative changes similar to those described in the other nerves, and the finer branches exhibited the same change.

In the muscle-spindles examined from the abductor pollicis no change could be found.

C. E. Beevor.

With regard to the first question put by Dr. Mott we must, I think, have a clear understanding as to what we mean by general paralysis and tabes being one and the same disease. I take it that what is meant is that we have a common cause which acts pathologically on different parts of the nervous system, and produces symptoms which are dependent on lesions of these parts, and which symptoms are liable to alternate according as these different parts are involved. It seems to me that to prove that the two sets of symptoms constituting tabes and general paralysis are really only symptoms of one and the same disease, we must have evidence that the tendency of one set of symptoms is to be followed or be associated with the other, *i. e.* that the majority of cases of tabes tend to take on the symptoms of general paralysis, and that the majority of cases of general paralysis tend to have tabetic symptoms. I use the word majority because it is the sum of the most constant symptoms which constitute a disease, and which enables us to recognise it when we meet with a certain group of symptoms.

Before going into the question of the frequency of the association of the two diseases we have to find out not only how many general paralytics have the symptoms and the pathological changes of tabes, but also how many cases of tabes become general paralytics. I would suggest that, as the valuable information in Dr. Mott's address is taken from the insane asylums, it shows us how many general paralytics have symptoms of tabes, and that we must go to other sources to answer the other side of the question.

Taking the question first as to how many cases of general paralysis have tabetic changes in the spinal cord, Dr. Mott states that in one half (thirteen out of twenty-six) "the posterior columns were affected, but only one was of the tabetic type."

From my own experience at the Queen Square Hospital, where the cases of general paralysis are seen in the earliest stages of the disease, I should say that in this stage they do not as a rule give symptoms of tabes with the exception of unequal pupils which do not react to light. The knee-jerks are in most cases

excessive, and they do not have lightning pains. As to how many of these cases develop other symptoms of tabes later on I have no personal experience, as one loses sight of them. With regard to the other side of the question, how many cases of tabes end in general paralysis, I think we must go to other sources of information.

In hospital practice it is often difficult to follow up one's cases of tabes to the end, as when they are unable to walk they cease to come to the hospital, and go to the infirmaries.

For the last fifteen years, owing to the kindness of Mr. J. R. Lunn, I have made periodic visits to the St. Marylebone Infirmary, and have had the opportunity of seeing there all his cases of diseases of the nervous system, but I do not remember to have seen a case of locomotor ataxy which has developed symptoms of general paralysis, and on writing to Mr. Lunn on the subject he has been good enough to inform me that he can only remember one case of general paralysis developing in a case of tabes during the nineteen years that he has been the medical superintendent, though they have had many cases of tabes.

Cases of tabes certainly do run their course to a fatal termination without showing any symptoms of general paralysis, though I admit that in these cases the cerebral cortex has not been examined to see if there be any loss of the tangential fibres or any changes in the cortical cells.

Taking therefore the question from the standpoint of tabes, I should say that although a few cases—as stated by Dr. Mott—have been met with which later develop well-marked general paralysis, it is the exception rather than the rule.

Another point is the slowness of progression of tabes as compared with that of general paralysis. All cases of tabes do not progress, and I have now under my care three cases which for eight to ten years have not progressed, and in whom the symptoms have hardly altered; if general paralysis was the same disease as tabes one would rather expect that the rate of progression in the two diseases would be similar.

With regard to Dr. Mott's second question, I regret that I have not any evidence to offer, and I can only accept Dr. Mott's authority in such matters.

It has, however, seemed to me difficult to explain that whereas in general paralysis the cells of the cortex, including the motor

area, are involved, in tabes the changes are almost entirely confined to the sensory side.

In other cases, for instance, like amyotrophic lateral sclerosis, where the cells of the motor cortex are attacked, it is the cells of the anterior horns, and not the posterior neurons, which are also attacked.

On Dr. Mott's third question respecting syphilis as a cause, I should say that I have not found the certain occurrence of this disease so frequent as I should have expected in tabes.

Out of thirty-nine of my cases there was a distinct history of syphilis in eleven cases, of a chancre without secondaries in seven, of gonorrhœa without a chancre in ten, of doubtful gonorrhœa without a sore in five, and no history of any form of venereal disease in six. What has struck me in these cases is that almost as many cases (ten) gave a history of gonorrhœa without a chancre, as of syphilis (eleven), while a considerable proportion (seven) gave a history of chancre without any secondary symptoms. I think that these data are reliable, for if a patient admits that he has had gonorrhœa, he would also probably admit syphilis. In the six cases without a history of any form of venereal it is not possible to speak definitely, as they may have concealed facts.

In the cases of general paralysis that I have seen, in the majority there has been a history of syphilis.

I have had two cases of juvenile general paralysis in which there was evidence of congenital syphilis.

In nearly all the cases where a history of syphilis was obtained, the disease was contracted ten or twenty years before the first symptoms of tabes showed themselves. The patients had not as a rule had any other manifestation of the disease, and had almost forgotten they had ever had it. In tabes, therefore, the symptoms certainly seem to occur after the mild cases of syphilis.

With regard to question four, as to whether the disease is due to the specific action of a poison upon peripheral nerve elements, it is difficult to give an opinion, and I do not quite understand how the question is to be settled, whether the cells decay because the terminals of the intra-medullary portion of the neurons are affected, or whether the latter waste because the cells are affected by the poison.

In concluding, I would say that general paralysis and tabes are dependent very largely, if not entirely, on the action of syphilis on different parts of the nervous system—parasyphilitic in nature—but as it seems to be the exception rather than the rule for tabes to be followed by general paralysis, I think that until it can be shown by *post-mortem* examination that the majority of cases of tabes present changes in their cerebral cortex characteristic of general paralysis, we can hardly look on them as one and the same disease with interchangeable symptoms, and I would rather regard them clinically as two diseases, which may occur at the same time in the same individual.

The question of prognosis is also much affected if the two are one and the same disease. If the majority of the cases of tabes are liable to develop symptoms of general paralysis, it makes the outlook very much more severe for these cases than if we look upon them as separate diseases; and though it is not possible to foretell that a patient may ultimately develop general paralysis, it is, I think, a very different thing from regarding the symptoms of general paralysis as those into which the patient with tabes will probably drift.

The question seems to me so very important, that I have made these remarks in the hope that Dr. Mott will be able to enlighten me, and to explain the difficulties which I have in looking on the two conditions as one and the same disease.

HENRY HEAD.

My remarks will be based on three separate lines of research, the results of which are as yet unpublished. (1) For the last eight years I have investigated the sensory disturbances in tabes, and have paid especial attention to the relation of such sensory disturbances to the visceral crises and joint affections of this disease. Although the work is far from complete, I hope you will pardon me if I allude to some of the conclusions to which I have arrived up to the present. (2) For the last five years Dr. Campbell, of Rainhill, and I have been working at the supply of the fibres that enter the posterior root-ganglia and the distribution of the afferent fibres in the spinal cord by

means of the lesions produced by herpes zoster. (3) I have been engaged in examining the characters of the cells which are found in the posterior root-ganglia at different levels of the cord. If we examine the course of an acutely degenerated posterior nerve-root, produced in man by the ganglionic destruction of zoster, in the monkey by the operator's knife, we find that the degeneration behaves somewhat differently in different regions of the spinal cord. In all cases at the point of entry into the cord the bundle at the head of the posterior horn, and the root zone that lies close to the posterior horn on its posterior aspect show degenerated fibres; but higher up in the spinal cord the appearance varies according to the level of the affected root or ganglion. If the degenerated root be one of the lower lumbar or upper sacral that supply sensation to the leg and sole of the foot, the degenerated fibres in their passage up the cord come closer to the median line of the posterior columns, and in the cervical region will be found to lie in Goll's column, as has been shown by Dr. Mott. If the degenerated root or injured ganglion be the first dorsal or one of the lower cervical group that supplies the arm and hand with sensation, it rapidly reaches the postero-external column, and can be traced into the posterior column nuclei of the medulla. On the other hand, if the injured ganglion lie between the level of the roots that enter the lumbar and those that enter the cervical enlargements, the degeneration is rapidly lost in its upward course and can be distinctly followed for about five segments only. Now, as Dr. Mott pointed out in his opening address, every posterior root that enters the cord may be said to consist of three sets of fibres. (1) A short spinal set; (2) a set of medium length fibres that reach Clarke's column and so pass to the cerebellum; and (3) of a longer set that pass up to the posterior column nuclei in the medulla, and thus transmit sensation to the cerebrum. Now the facts I have just brought forward point to a difference in the relative number of these groups of fibres in different regions of the cord. In those roots which supply sensation to the limbs, the longest fibres are relatively in the majority; whilst in those which subserve the sensation of the trunk, the number of long fibres is relatively less, and the short spinal group preponderate. If we now examine the constitution of a posterior root-ganglion, we find that it consists, as Dogiel and others have pointed out,

of at least two different types of cells: the one large, spherical in shape, with coarse granules, and with a most remarkable spiral process ending at a considerable distance from the cell in a T-shaped junction; another type, smaller, more pear-shaped, and containing much finer granules, which ends in a straight process that branches dichotomously. These are the two preponderating types of cell, but there are several other forms which occur in less number. So far my results simply confirm those of Dogiel and others, but my attention has been less attracted to the finer details of these cells than to their original distribution in the central nervous axis, which seems to have escaped other observers as far as I can discover at present. On examining the distribution of these two types of posterior ganglion cells at different levels by Dogiel's modification of the intra-vital method and Nissl's method, I think it may be said that up to the present the following conclusions are correct. And in speaking of large cells, let me be understood to mean cells with large deeply-staining granules, a spiral process, and a T-shaped branch; by small cells, cells more nearly pear-shaped, with smaller granules staining more diffusely, and a straight branching process. In the region of the cervical and lumbar enlargements, that is to say, in the fifth, sixth, seventh and eighth cervical and first dorsal ganglia, and in the third, fourth and fifth lumbar and first and second sacral ganglia, large and small cells are found, but the large cells are in great excess. On the other hand, in the dorsal region the small cells are in much greater number; then the large cells and such a ganglion as the seventh or eighth dorsal will show them in their purest form. Not that at any part of the axis is one form of cell absent, but at the level of the limbs the large cells much increase in number, whereas over the great visceral sensory area of the trunk the posterior root ganglia contain mainly small cells. Thus the conclusion lies near at hand that the smaller cells are associated with the shorter spinal group of fibres, whereas the long fibres of the postero-median and postero-external columns are associated with the large cells of the ganglia in the region of the cervical and lumbar enlargements. Now Münzer and Wiener in the first November number of the 'Neurologisches Centralblatt' of 1899 have shown by most ingenious experiments that the long paths of the posterior columns do not conduct painful impressions,

and that the painful sensations are conducted by shorter fibres that enter the cord by the posterior roots. Let us now turn to the condition of sensation in cases of tabes dorsalis. I can confirm in the most complete manner the statement of Fraenkel and others, that if ataxy is present the only essential loss of sensation is a loss of the sense of passive position. But I wish to warn those who would repeat these results that the sense of passive position must be tested with certain precautions that I have not found in general use. The toe or finger to be tested must not be grasped by the dorsum and plantar or palmar surface, but must be grasped laterally. For by this means a patient whose sense of touch is good can no longer discover the movement that is being produced with the aid of his intact sense of touch. Secondly, we must be very careful to prevent his contracting the long muscles of the toe or finger, and thus discovering into what position it has been moved should he still retain some muscular sense. If these precautions are taken, it will be found that whenever a tabetic falls with his eyes shut or shows definite ataxy, there is some loss of the sense of passive position in the terminal joints of the affected limb. I will now throw upon the screen the cord of a patient who suffered from abductor paralysis of the larynx. His knee-jerks were absent, but absolutely no form of sensation was affected except the sense of passive position in the fingers and toes, especially in the thumb and great toe. He later developed a Charcot's knee on the left side, and died suddenly from rupture of a small aneurysm of the posterior part of the arch of the aorta. Yet you will see how profound a degeneration affects the long tracts of the cord, although the man's condition was such that many observers refused to believe he was suffering from tabes. If, on the other hand, we turn to those cases where some form of sensation other than the sense of passive position is lost, we find a marked difference in the symptoms of disease according to the form of sensation mainly affected. On the one hand, the sense of light touch (cotton wool) may be profoundly lost over a wide area of the limbs and trunk, and provided that this is the only loss of sensation the patient will be extremely ataxic, but will not suffer from visceral crises (gastric, intestinal, vesical, or rectal). If the sense of painful stimuli only is lost—and such cases, though uncommon, have particularly attracted my attention,—visceral

crises are certain to be present, and ataxy will be a prominent feature solely according to the extent to which the analgesia is accompanied by loss of sense of passive position in the joints. A commoner form of this type is one where the analgesia is accompanied by more or less loss of the sense of cold, and perhaps of the sense of heat. Such cases, however, still belong to the second or visceral type, because the concomitant loss of the sense of heat and cold seems to make no difference to the gross phenomena of the disease. Thus, to sum up the effect produced by the various disturbances of sensation which may accompany tabes, I think I may say: (1) The ataxy, in so far as it is due to loss of sensation, and not to loss of muscular tone, is primarily due to a loss of the sense of passive position in the terminal portions of the limbs. Until this loss of the sense of passive position makes its appearance the case remains in the pre-ataxic stage, however much alteration in the sense of pain, heat, or cold may be present; (2) loss of touch only produces an increase in the ataxy; (3) loss of pain in no way affects the ataxy, but is associated with the visceral disturbances that we know as crises; (4) loss of heat or cold, or of both heat and cold, produces no gross change in the form assumed by the disease. Thus it is obvious that the disease process at the bottom of tabes dorsalis is one that picks out different elements in the afferent system, and cannot be due to so gross an anatomical lesion as meningitis around the point where the roots enter the cord. It probably affects the whole nerve element, and whether or no gross changes are present in the ganglion-cells, depends upon whether the peripheral end-organs are profoundly affected or not, and in no way on the extent of the affection of the fibres in the posterior columns. In the process of destruction of the nerve elements, paroxysmal outbursts will occur which will assume the character of the element that is undergoing destruction. Thus destruction of the elements that subserve the sense of position will be accompanied by those paroxysmal outbursts of acute ataxy that are not uncommon in the course of tabes. Destruction of the elements that subserve pain impressions will tend to be accompanied by hyperalgesia of the superficial structures of the body, and a disturbance in the functions of the viscera which are supplied from the same segments, according to the laws that have been laid down in my work on referred pain in

visceral disease. Such disturbances constitute the well-known visceral crises, and I believe it is possible, by watching the areas on the skin that show evidence of advancing destruction in their sensation to pain, to predict what form the visceral crises will assume. On the other hand, in general paralysis of the insane, destruction of the nerve elements of the motor cortex is accompanied with a paroxysmal disturbance known as a convulsive seizure. The crises of tabes, and the seizures of general paralysis, are due essentially to the same process affecting different nerve elements in the central nervous system. Both are parasyphilitic diseases, and the more one watches the two, the more certain one becomes that they are due to an identical process affecting different portions of the nervous system.

PURVES STEWART.

I propose with your permission, Sir, to discuss three questions: Why is it that some cases of syphilis escape without any affection of the nervous system whatever, whilst other syphilitic patients become tabetics or general paralytics? Secondly, why do some syphilitic patients develop tabes, whilst other syphilitic patients develop general paralysis? And lastly, why do we sometimes find the lesions of tabes in certain non-syphilitic patients, for example in pernicious anæmia?

The answer to these questions is not to be found in the intensity of the previous attack of syphilis, for it is well known that the severity of tabes is in no way proportional to the previous attack of syphilis. A slight case of syphilis is just as likely, as Dr. Beevor said, indeed sometimes more likely, to be followed by tabes than one that is severe. Severe cases of syphilis may sometimes escape altogether. Obviously, therefore, there must be some other factor which determines the occurrence or non-occurrence of tabes and of general paralysis. And that factor, as has been pointed out by Edinger of Frankfort, is very often found to consist in over-exertion of certain definite groups of nerve-cells. Briefly stated, on this theory tabes is the result of over-exertion of certain nerve-paths in an individual whose nervous system is below par, commonly from syphilis, sometimes from a less common cause, as for ex-

ample, pernicious anæmia. Such a simple theory is obviously capable of proof or of disproof, and with the view of proving or disproving this Edinger undertook certain experiments, and the lantern-slide shows the result of one. Edinger and Helbing produced experimentally lesions similar to tabes in the spinal cord and posterior nerve-roots of rats. They took a certain number of rats and made them run in a treadmill every day, all day long, for various periods from ten weeks downwards. Other rats they hung up by the tails, by sticking plaster, for three hours every day for a similar number of days. Certain other rats were rendered artificially anæmic by the subcutaneous injection of pyrodin. The spinal cords of these rats, and also the posterior nerve-roots, on examination by the Marchi method were found to show distinct degeneration, which, as you see in this diagram, is most marked in the posterior columns. The spinal cord of the rat which ran seventy-two days in the treadmill you can see with the black spots much more numerous in the posterior columns than anywhere else. These degenerative lesions were much more marked in the anæmic rats than in the healthy.

Clinically a certain amount of evidence points in the same direction. It is well known that tabes is commonest in those people who habitually throw a great strain on their static apparatus, that is to say, the nervous paths which commonly become exhausted first are the nerve-paths which subserve the sense of equilibration. We all know that tabes is much commoner in men, who habitually walk about a great deal, than in women, who live a more sedentary life. Moreover Edinger has pointed out a very important clinical fact, namely, that in many cases of tabes, immediately before the first symptom of the disease has appeared, the patients give a history of some special over-exertion. And the clinical type of tabes differs according to the particular functions which have been over-exerted in each case. Thus one man, a hospital patient at Queen Square, was a draper. He failed in business. Previous to this he had been able to drive about in cabs and similar luxurious vehicles. After he failed in business he had to walk about a great deal, and a few weeks after that he developed ataxia of the legs. Another patient at Queen Square, a commercial traveller, from motives of economy began to walk a good deal in order

to save his fares. He also shortly afterwards developed ataxy of the legs. Another patient, a solicitor, was driving in a cab one day, when he got pitched out and hurt his back. Immediately afterwards he became very ataxic. I think a still more instructive case was that of a woman at Queen Square who was a lace-maker. She used to sit to do her work. For some reason she was transferred to another part of the building, where she had to do her work standing. A week afterwards her legs began to give way and she would sometimes fall down. All these cases were probably syphilitic. Edinger has recorded the case of a physician who had an Argyll-Robertson pupil in one eye, and that eye, according to Edinger's statement, was the one which he habitually used in working with the microscope. Edinger also reports the case of a tailor who used to sit all day at his work. He became markedly ataxic in his legs, and was triumphantly pointed out to Edinger (by those who thought his theory wrong) as a case disproving it. But Edinger found that this tailor lived at the top of five flights of stairs which he had to climb and descend in order to get to his work.

I submit that a similar explanation holds good for many cases of general paralysis.

It is a familiar fact that general paralysis is commonest in men who lead lives, or who have led lives, of mental excitement or stress, either physiological or due to excesses, and the greater frequency of general paralysis amongst men rather than amongst women is in favour of this view. I have inquired into the cases of general paralysis at Queen Square Hospital which I have had the opportunity of observing, and I have found that in a certain number of them there was a distinct history of some acute mental strain preceding the immediate onset of the first mental symptoms. Thus, one man, an Army pensioner, who had both tabes and general paralysis, developed his first mental symptoms after the stress of working for an army examination. He had had syphilis. Shortly after this examination he began to have fits. A second man was one who went to Australia, and in the course of his life there tried to become a schoolmaster. He had in his class a succession of very noisy boys, and the mental strain was so great that he had fits. When he came back to Queen Square he was a typical general paralytic. A third case was that of a young girl whom

Dr. Mott included in his statistics, a general paralytic. She suddenly learnt one day that her lover was a married man. The shock of that discovery was so great that she immediately afterwards became violently mentally affected, and ultimately died of general paralysis. She was a congenital syphilitic. Such cases might easily be multiplied.

Finally, if it be the fact that physical over-exertion can precipitate an attack of tabes, and that mental over-exertion or mental excitement can precipitate an attack of general paralysis in a patient who is previously debilitated by syphilis or other predisposing disease, it is possible perhaps to do something to prevent tabes and to prevent general paralysis. We should, therefore, advise every syphilitic patient to abstain from severe physical exercise in order to avoid tabes, and to abstain from excessive mental excitement or worry in order to avoid general paralysis.

ROBERT JONES.

I would like first to express my great satisfaction and interest in the address given by Dr. Mott. Dr. Mott states as his opinion that there is not sufficient evidence to prove that if there were no syphilis there would be no general paralysis or tabes. Dr. Ferrier went further, however, in saying that if there were no syphilis there would be neither of these diseases; in support of this he cited the inoculation experiments of Krafft-Ebing. In these experiments general paralytics were inoculated with syphilitic virus, and as no reaction ensued, the conclusion was that the patients had previously been infected with syphilis. But does the general paralytic react to anything in the later stages of his disease? He passes through stages of pulmonary gangrene and phthisis, without cough, expectoration, or elevation of temperature. He is the subject of bedsores, septicæmia, pyelitis or peritonitis, without fever. These facts have to be taken into account in connection with Krafft-Ebing's experiments.

Again, as to the cerebral lesion, in syphilitic disease of the brain the lesions are usually—

(1) In the blood-vessels of medium size, endarteritis; in the smaller vessels, periarteritis.

(2) Diffuse meningeal infiltration.

(3) Gummata.

But the arteritis and meningitis are commonly basal, whereas the lesion of general paralysis is cortical and appears to me more of a diffuse vascular meningo-encephalitis, a variety of interstitial inflammation or peri-encephalitis.

General paralysis and tabes in association are not so very common. Out of 520 autopsies on general paralytics at Claybury during a period of about six and a half years, (409 males, 111 females), the proportion of tabetic cases was not above 2 per cent.

I have long been acquainted with the variety of general paralysis known as the tabetic, and have long looked for some definite and constant symptom, such as the ataxic gait; but this may not be present, or if present, may give way to the paretic or spastic.

I do not deny the importance of syphilitic antecedents; by syphilis a way is opened up for the action of other ætiological factors such as alcohol, sexual excess, mental overstrain, or a combination of these which is apt to be overlooked.

BERTRAM ABRAHAMS

concurred with the general testimony to the importance of Dr. Mott's researches and the value of the results detailed in his address. He submitted, however, that to apply the metasyphilitic or parasyphilitic theory to every case of tabes and general paralysis, as was done, for instance, by Hirschl, was carrying it too far in the light of our present knowledge. The authentication of a single non-syphilitic case of either disease must direct attention to the elucidation of other causes. Dr. Mott had conclusively shown the necessity of the syphilitic factor in the ætiology of infantile general paralysis, but was this factor equally certain in the adult form of this disease, or even in tabes? Looking at the question from the most general point of view, it appeared to be one mainly of vitality. Every cell in the body started life with a certain measure of vitality, and the syphilitic poison possessed the power of diminishing the vitality in the case of certain organs, particularly the central nervous system. Such shortening of cell life as resulted might also arise from congenital

or sporadic causes, as in pseudo-hypertrophic muscular atrophy, Friedreich's disease, etc. The syphilitic factor was thus a most important one in the production of neuronic degeneration, but it was not the sole one. Strain was also to be reckoned with, and they had only to consider the pathology of arterial degeneration to see how important a part it might play in the local determination of syphilitic sequelæ. With regard to general paralysis there was evidence in the same direction. This disease was known to particularly attack persons of considerable mental activity, and the strain upon the association neurones no doubt rendered these especially prone to selection by the syphilitic virus. An almost experimental example was afforded by the American negroes, among whom general paralysis was practically unknown before their emancipation, since when it had become very common. Syphilis had not increased among them, and the irresistible conclusion was that the appearance of general paralysis was a result of the increased nervous strain consequent upon entering actively into the struggle for existence. But strain alone might cause arterial degeneration, and so there seemed no reason why it should not lead to a loss of neuronic vitality. It might be that in cases of general paralysis in which a syphilitic history was absent, excessive mental strain, often added to toxic agents such as alcohol, might be sufficient to account for the disease. What ætiological factor determined the tabetic lesion to the posterior columns was at present unknown, and indeed our knowledge of the causes other than syphilitic of this disease was almost *nil*. One argument which seemed to tell in favour of the syphilitic origin of both diseases was their relative uniformity of pathological type. Typical cases of both were known to arise after syphilis, and it was certainly unusual, though not unknown, for various toxic agents to produce identical results upon the nervous system. If one case was syphilitic, the probability would be in favour of all being so; but there was no essential reason why different pathological agents should not lead to the same effects. With regard to the relation of tabes to general paralysis little could be added to what Sir William Gowers had said. An ætiological identity could hardly be used to connote "the same disease," and hence the question came back to the former one, namely, as to whether all cases of tabes and of general paralysis were syphilitic or not.

What was abundantly shown by Dr. Mott's work was the pathological similarity of the two diseases, in that each of them was primarily a neuronic degeneration and not an interstitial overgrowth. This was confirmed in the syphilitic cases by the length of time which elapsed between the specific and nervous manifestations. In the twenty years which might pass before a syphilitic subject developed tabes every trace of toxin must long since have been eliminated. What happened was that the neurones were affected at the time of the syphilis in a manner not to be detected by present microscopical methods, but revealing itself inevitably in their diminished vitality and premature death.

FLETCHER BEACH.

It appears to me that in the discussion which has been going on with reference to Dr. Mott's paper, very little attention has been paid to juvenile general paralysis. I can give no observations on the relation of juvenile tabes to juvenile general paralysis for the reason that I have had no experience of juvenile tabes. I have, however, had under my care two cases of juvenile general paralysis, one a girl aged seven years, the other a boy aged eight years, and on consulting the literature of the subject I find that several such have been recorded. The first case which I have found reported was that of a girl in whom the disease commenced at the age of fourteen. It was reported by Dr. Clouston, and was published in the 'Journal of Mental Science,' in October, 1877. There is said to have been a previous case reported about twenty years previously in 'Braithwaite's Retrospect,' but I have been unable to find it, so that for practical purposes I regard Dr. Clouston's case as the first on record. The next case was that of a boy, in whom the disease made its first appearance at the age of twelve years, and was reported in the same journal in October, 1881. To save trouble, I may mention that all the cases to which I have to refer or allude, with the exception of my own, have been published in the 'Journal of Mental Science;' with four exceptions they all occurred in the United Kingdom. The next case was that of a girl in whom the disease was first noticed at

fifteen years of age, and was reported in July, 1883, by Wiglesworth. On going fully into the details of these three first cases, it was noticed that there were no grandiose symptoms, but a steady progress towards dementia. The motor symptoms were well marked, and in two of the cases the course of the disease was prolonged. There was a hereditary history of neurosis in all the cases, but in two of the three cases it was distinctly stated that there was no history of syphilis. In the discussion which followed Dr. Wiglesworth's paper, the various speakers mentioned that they had altogether seen eight cases. There was also a case which I omitted to mention, in which general paralysis appeared in an imbecile, but whose age was not stated, and which was recorded by Dr. Kohler. In 1891 Dr. Clouston described two cases of what he named "Developmental General Paralysis." One of these commenced at fifteen, and the other at fourteen years of age. Both were girls, who were childlike in appearance. There was arrested bodily development in each case, as well as arrest of all symptoms of puberty, since they had never menstruated, and the breasts were undeveloped. In both cases there was a history of syphilis and of neuroses in the parents. Dr. Clouston regarded them as cases of general paralysis "due to hereditary syphilis as a predisposing cause, and to puberty as the exciting cause, with a neurotic heredity as an extra predisposing cause, the disease having a distinct kinship hereditarily and developmentally to the other neuroses of this period of life."[1] Apparently the putting forth of nervous energy for the production of reproductive life caused a strain, and so induced general paralysis in the same way that outputs of energy constitute a strain in adult life.

Since 1883, when Dr. Wiglesworth's paper was read and discussed, I find that twenty-four cases have been referred to or fully recorded, so that, including Dr. Clouston's two cases already mentioned, altogether thirty-six cases have been mentioned by various authors. If to these be added my two cases we have a total of thirty-eight cases of juvenile general paralysis. The actual age at which the disease was first noticed was stated in twenty-one cases, and the greatest number (no less than eleven) occurred during the ages of fourteen and fifteen. The age of the youngest on record was seven, and that of the oldest

[1] 'The Neuroses of Development,' 1891, page 90.

sixteen. The fact that eleven cases occurred at the ages of fourteen and fifteen seems to add strength to Dr. Clouston's theory.

As regards the question of syphilis in the parents being the cause of juvenile general paralysis, I find that there are twenty-five cases in which the histories are given, and of these twenty-five twenty have a history of congenital syphilis. Of the five cases in which there was no history of syphilis there was a history of neurosis in the parents in two, and of alcoholism in the father in two. It appears, therefore, that congenital syphilis is the chief factor in the production of juvenile general paralysis, and the same conclusion is arrived at by Dr. Campbell, of the Rainhill Asylum, Lancashire.

Lately the question of congenital general paralysis has been brought forward by Drs. Macdonald and Davidson of the Dorset County Asylum. In a paper read by them at the Portsmouth meeting of the British Medical Association this year, they relate three cases of what they consider to be congenital general paralysis. There was no history of parental syphilis in any of the cases, though the point was specially made the subject of inquiry; but there was a strong neuropathic taint in all of them. It is certainly a question which requires further attention being paid to it.

Summing up, I would say that juvenile general paralysis is commonly, but not universally, due to congenital syphilis, that as a rule there are no grandiose symptoms, but a steady progress towards dementia, and that the course of the disease is prolonged in juvenile cases. In six cases mentioned by Dr. Shuttleworth, as well as in my own, there was a history of congenital syphilis, and as usually happens in such cases, dementia came on at the time of the second dentition, or at the age of puberty.

There are many interesting points connected with the question of juvenile general paralysis, but the want of time does not permit me to mention them.

F. W. Mott, F.R.S.

Before replying to the criticisms which have been made upon certain points in my paper, I should like to take the opportunity of thanking the distinguished neurologists and pathologists who

have taken part in the discussion, and especially I wish to express my grateful acknowledgments to Dr. Buzzard and Sir William Gowers for the very kind references they have made to my work in the pathological laboratory of the London County Asylums. It is particularly satisfactory to me to find that the views which I have expressed have been in the main endorsed by those who have taken part in this discussion. It would, however, have been evidence, to my mind, of failure in opening the discussion had I not evoked difference of opinion.

All the speakers have endorsed the generally accepted view that syphilis is the preponderant factor in the production of tabes, and although the evidence is not so easy to obtain, on account of the mental condition of the patient, it seemed to be pretty generally accepted that syphilis is also the preponderant factor in general paralysis. I was led to believe from Sir William Gowers' address that he considered the evidence in favour of the exclusive origin of tabes from syphilis as being stronger than that of general paralysis. With regard to this, I was particularly glad to hear the emphatic statement of Dr. Ferrier, who from his large experience came to the conclusion that if there were no syphilis there would be no general paralysis or tabes, and that from clinical observation they were essentially identical. The remarks of Dr. Head upon this point I would endorse, and I have pointed out in the 'Archives of Neurology' the relationship between the pains and visceral crises of tabes and the epileptiform seizures of general paralysis, both indicating the increased irritability, prior to death, of systems of neurones having special functions. I would entirely agree with Dr. Buzzard, Sir William Gowers, and others, who maintain that tabetic symptoms more often precede the symptoms of general paralysis than the converse. I have, however, seen cases in which mental symptoms indicating the prodromal, or even the first stage of general paralysis have preceded the tabetic. I made quite recently an autopsy on a patient, a policeman, who eighteen months before he had any signs of tabes, exhibited mental symptoms in the form of irritability of temper, absent-mindedness, and depression.

Dr. Buzzard related a most interesting example of disease in husband and wife, the former infecting the latter with syphilis. I showed at that meeting a photograph of husband and wife,

the latter of whom was affected with general paralysis, the former with its tabetic form. The man died last week, and I was able to verify the diagnosis. The fact that the wife had healthy children by her first husband, and no children by her second, is important. The man himself presented well-marked signs of syphilis, and I have no doubt that he infected his wife, and that the syphilitic virus was the essential cause of the disease in this married couple. Several instances have been previously recorded of a similar nature, and they tend to show that general paralysis is dependent upon syphilis. There seem to be two opinions held by the speakers who have taken part in this discussion as to the relationship of syphilis to general paralysis. All admit that syphilis is the preponderant factor, but some would agree with Dr. Savage that other poisons, such as lead and alcohol, might cause a similar degenerative process. Dr. Ferrier, however, concludes with Hirschl that, if there were no syphilis there would be no general paralysis. This may be true, although I do not say it is proved. The arguments, however, are very strongly in favour of this doctrine, and recent experience teaches that a syphilitic history can be obtained (as Dr. Campbell, of Rainhill, shows) in a far larger number of general paralytics than was previously believed. The experiments of Krafft-Ebing give a very strong support to this view, but perhaps the strongest argument is the fact that juvenile general paralysis can be *proved* to occur nearly always in the children of syphilitic parents. Again the fact that general paralysis affects both sexes equally where the chances of obtaining syphilis are equal, as in the inherited disease, is corroborative of the same view. Sir William Gowers remarked that he had not seen any such cases, although he had observed impairment of cerebral function as a consequence of inherited specific disease. I have now seen thirty cases, and a study of these assures me that the disease is both clinically and pathologically identical with the adult form. Dr. Payne spoke of the fibrosis of liver and kidneys induced by syphilis. In three of these cases the liver was so affected. But what was very remarkable was the different way in which the syphilitic poison affected different individuals of the same family, leading me to suppose that an exciting factor usually comes in to determine the seat of the disease. Sometimes the history suggests that the

parental germinal plasm is unequally affected by the toxine, *e. g.* I have seen a juvenile general paralytic die without having presented any signs of syphilis on the body, whilst a younger sister had well-marked Hutchinson teeth, rhagades, and double keratitis. Two brothers were affected. The elder, who died of acute general paralysis, was an able-bodied seaman, his illness dating from the Fashoda crisis: he showed no external marks of syphilis on the body, but his liver was characteristically fibroid. The younger of these two brothers had Hutchinson teeth and saddle-shaped nose; his growth was stunted, and he was an imbecile in Caterham Asylum. I could multiply similarly instructive instances. I cannot help thinking that the poison acts by inducing a premature progressive decay of certain systems of neurones, selecting the afferent spinal projection and the cerebral motor association systems. I was glad to hear that Sir William Gowers has long maintained the view which I put forward to explain this progressive decay, viz. an inherited or acquired loss of durability due to the influence of the syphilitic toxine. In trying to solve the problem why special systems of neurones undergo degeneration when subjected to the action of the syphilitic virus, we have to consider first the possibility of a selective action of the poison itself. We know that many poisons have a selective action upon groups or systems of neurones, *e. g.* tetanus has a predilection for the motor nucleus of the fifth nerve. Again we have to consider the influence of stress, and Clouston, who first described juvenile general paralysis, called it developmental paralysis. The disease usually develops just after puberty, at a time when new emotions, passions, ambitions, and disappointments, associated with the awakening and development of the sexual instinct, originate a new psychical existence, involving widespread cerebral activities and increased bio-chemical change; but it may begin long before puberty or many years after it. Nevertheless there is considerable reason for believing that stress does determine the seat of disease, and I am glad to take this opportunity of pointing out how strongly Professor Edinger has long advocated this view, and (as you have heard Dr. Purves Stewart state) he has demonstrated experimentally the effect of stress upon the posterior column of the spinal cord in anæmic rats. The question whether general paralysis and tabes are one and

the same disease, or one and the same morbid process affecting different parts of the nervous system, is, as Sir William Gowers says, rather a question of words. However, we should study disease for the purpose of its prevention and cure, and the example cited by him of tubercular tumour of the brain and pulmonary phthisis being regarded as one disease, is, I think, a most apposite one. For as all measures which will tend to get rid of the tubercle bacilli will tend to prevent both of these conditions, so likewise all measures which tend to prevent the prevalence and spread of syphilis, will diminish the frequency of tabes and general paralysis. I can only say that everything in my experience tends to show that general paralysis and tabes are one and the same morbid process affecting different parts of the nervous system. It was asked, if this be so, how do you explain the fact that in general paralysis it is the brain, and especially one particular part, which is affected, while in locomotor ataxy it is the cord. I was glad to find Dr. Hale White support the answer which I should make to this question. If we consider the effects of poisons like alcohol, lead, ergot, lathyrus, and diseased maize (pellagra), they may produce both peripheral nerve and cord changes, together with cerebral changes, in the same subject. It is the individual, his inherited tendencies, his occupation and habits, which determine the seat of the morbid process. In some cases, however, the cord symptoms predominate and the cerebral may be slight, or even absent; on the other hand—and these are the cases of lead and alcoholic poisoning which come into asylums and are not seen in hospitals—we see the cerebral symptoms predominant and the paralytic symptoms often less defined, overshadowed by the brain affection or even absent. So it is with general paralysis. Cases come into hospitals with Argyll-Robertson pupils, marked paresis, and speech affection, but with the mental symptoms only comparatively slightly developed. Numerous cases of tabes, likewise, attend hospitals for a considerable time, and then marked mental symptoms develop, when the case is certified as one of tabetic general paralysis. As to whether the morbid process in general paralysis and tabes should be regarded as primarily inflammatory or not, is a question which I will now attempt to answer. Dr. Alexander Bruce has referred to the views of Obersteiner and Redlich, and Dr. Batten apparently supported the same. Sir William Gowers

has given many weighty arguments against it, the most notable being that "we cannot explain limitation by a process essentially random in incidence with differentiated sensory affection." The constriction theory, moreover, will not explain why certain fibres of the posterior root are attacked before others; it does not explain grey atrophy of the optic nerves, the reflex irido-plegia, the temporary and permanent partial paralysis of the ocular muscles, the early affection of the peripheral nerves of joints in Charcot's disease. But a still graver objection is that only in very late cases is there any pronounced evidence of meningitis, and then the thickening of the membranes is marked wherever there is sclerosis and atrophy, even over the direct cerebellar and the antero-lateral tract (when these are affected), as I showed at the first meeting. In rapid cases there is little thickening of the membranes and no affection of the vessels. Again, I have examined twelve cases of tabetic cords, and in every case, whether the disease was rapid or slow, I have found some changes in the posterior roots as far as the ganglion. I showed, moreover, specimens of very marked cerebro-spinal syphilitic meningitis, in which I could find no degeneration in the posterior columns. I do not, however, deny that possibly there is a precarious blood-supply normally in the posterior columns as compared with the rest of the cord, and I think it is this which determined exclusive degeneration in this region in Dr. Batten's cases of cerebral tumour. Lissauer's tracts, in his cases, were not affected; whereas in tabes they are the earliest to be so. I do not deny, again, that vascular changes are present (possibly from the first) in the regions of the brain affected with general paralysis, but the wasting here always attacks the frontal and central convolutions, and spares, comparatively speaking, the occipital and temporo-sphenoidal. The area wasted corresponds very much, though not entirely, with the distribution of the internal carotid; it corresponds even more closely, as I have shown, with the area drained by veins opening into the longitudinal sinus, and I think these facts are of importance in explaining the excessive atrophy and subsequent pia-arachnoid thickening of these regions owing to anæmia and venous congestion. I have recently had the opportunity of showing at the Society the intense chronic inflammatory changes around the vessels and in the membranes in two cases of Congo sickness;

in neither of these was there the disorganisation of the cells met with in general paralysis, although the perivascular changes were more marked than I have ever seen them in the last-named disease.

In conclusion, an important point was raised by Dr. Buzzard, in connection with the relation of the soft sore and these two degenerative processes of the nervous system. I quite agree with him that there is very often a history of soft sore, and in my experience gummatous processes and tertiary lesions are not frequent in tabes and general paralysis. I think that very probably these so-called soft sores are really modified syphilitic lesions. Hitzig has also called attention to the frequency with which the soft sore is followed by these parasyphilitic affections, and he holds that there are possibly several poisons present. Moreover, have we not an analogy in diphtheritic paralysis, for here the mild and unsuspected cases are frequently followed by nervous sequelæ,—indeed the latter may be the first evidence that the patient has suffered from diphtheria?

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